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Flow Synthesis of Coumalic Acid and its Derivatization

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1 Experimental

1.1 Equipment and materials

Solvents were obtained from Fisher Scientific, and H₂O was deionised before use. MeOH (analytical reagent grade) and MeCN (HPLC grade) were used as supplied.

¹H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) or a Varian VNMRS-700 (700 MHz) spectrometer. Chemical shift values are given in units δ relative to residual protic solvent. The multiplicity of the signal is indicated as: br – broad, s – singlet, d – doublet, t – triplet, q – quartet and m – multiplet, dd – doublet of doublets, dt – doublet of triplets, etc. Coupling constants (*J*) were measured to the nearest 0.1 Hz.

¹³C NMR spectra were recorded on a Bruker Avance-400 (101 MHz) or a Varian VNMRS-700 (127 MHz) spectrometer with broadband proton decoupling using the deuterated solvent as the internal deuterium lock. Chemical shift data are given in units δ relative to the residual protic solvent.

Liquid chromatography-mass spectrometry was performed using a TQD mass spectrometer (Waters UK, Ltd.). Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of MeCN–water containing 0.1% formic acid. Gradient = 0–1 min: hold MeCN 5%, 1–4 min: ramp MeCN 5–95%, 4–5 min: hold MeCN 95%, 5–7 min: ramp MeCN 95–5%, 7–8 min: hold MeCN 5%. Retention times are reported as *R_t*. High resolution mass spectra (HRMS) were recorded on a Waters Acquity LCT premier XE spectrometer using time of flight with positive electrospray ionisation (ESI⁺). The masses reported are those containing the most abundant isotopes (⁷⁹Br).

Infrared spectra were measured on a Perkin-Elmer Paragon 1000 FT-IR spectrometer fitted with a Diamond attenuated total reflection (ATR) accessory (Golden Gate). Letters in parentheses refer to the relative absorbency of the peak: w – weak (<40% of the most intense peak), m – medium (40–75% of the most intense peak), s – strong (>75% of the most intense peak).

1.2 Experimental configurations of the flow reactors

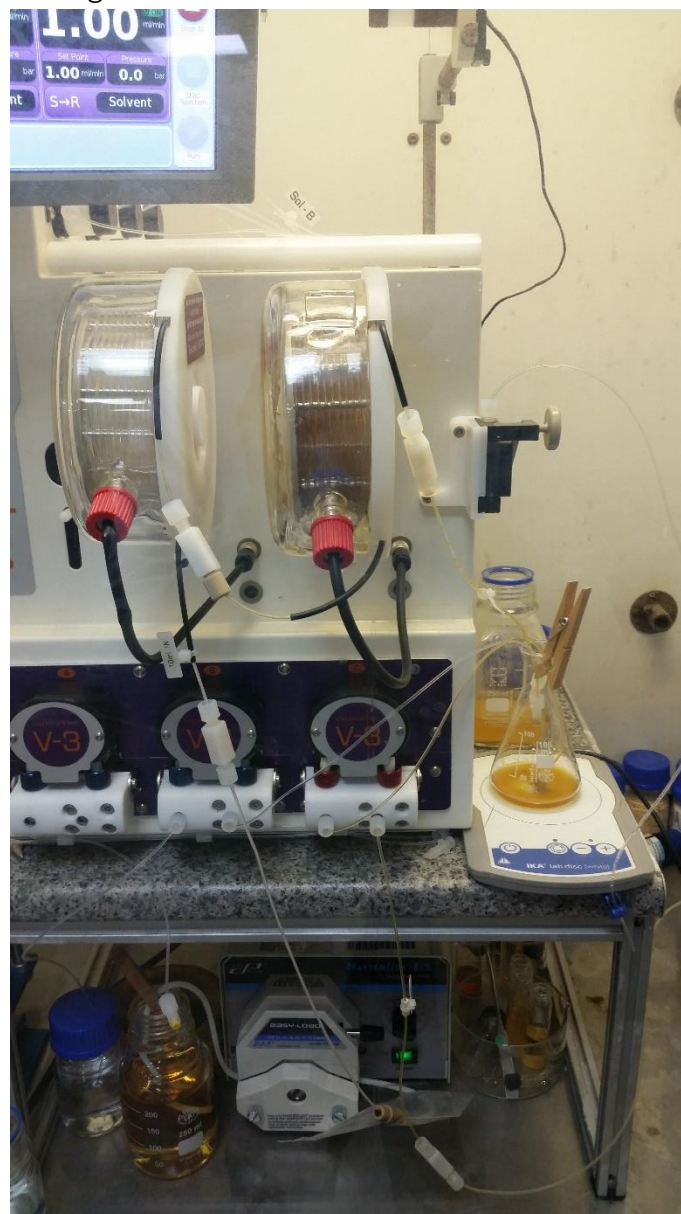


Figure S1 – Configuration of the Vapourtec flow reactor for the synthesis of coumalic acid.



Figure S2 – Configuration of the Vapourtec and Polar Bear flow reactors for the synthesis of methyl coumalate.

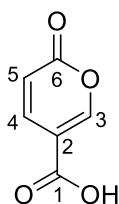


video of MA to CA
slow - Copy.mp4

1.3 Continuous flow syntheses for coumalic acid and methyl coumalate

Optimisation reactions were carried out in a Vapourtec E-MedChem reactor system coupled with a Masterflex L/S external peristaltic pump with Masterflex C-Series tubing (size 13). Stock solutions were prepared at a concentration of 100 g malic acid per 200 mL of concentrated H_2SO_4 (3.73 mol dm^{-3}) and heated at 40°C for 30 mins immediately prior to reaction to ensure the malic acid has fully dissolved (note: reaction does not occur at this temperature). The stock solution was then pumped at a defined flow rate into two sequential 10 mL PFA reactors heated to 120°C (3 mins residence time). The product stream containing the crude coumalic acid was collected into a flask, to which methanol was constantly added *via* a second pump at a defined flow rate. This stirred solution was pumped at a defined flow rate into a 8.25 mL Polar Bear Plus reactor heated at 90°C (9 mins residence time). The exiting product stream containing methyl coumalate was collected as a batch and quenched and H_2O was added, resulting in the formation of a precipitate of the crude product which was isolated by filtration.

1.4 Coumalic acid

Chemical Formula: C₆H₄O₄

Exact Mass: 140.01

Example batch procedure:

Malic acid (200.0 g, 1.49 mol) was charged to a 1 L RBF fitted with a stirrer. Concentrated sulfuric acid (400 mL, 7.50 mol) was charged to the RBF. The resulting slurry was heated at 90 °C with stirring for 6 h, during which time significant foaming was observed. The orange solution was allowed to cool to RT, then poured onto ice (900 mL), and stored in the freezer overnight. Formation of a yellow precipitate was observed. After filtration and washing with H₂O, the wet solid was dried on top of an oven (temperature approx. 50 °C) before drying under vacuum. The crude material was isolated as a pale yellow solid.

Isolated yield: 50.8 g (362.8 mmol, 49%).

¹H NMR (700 MHz, d⁶-DMSO): δ/ppm 6.37 (1 H, dd, *J* = 9.8, 1.1 Hz, H2), 7.77 (1 H, dd, *J* = 9.7, 2.6 Hz, H3), 8.49 (1 H, dd, *J* = 2.6, 1.1 Hz, H5);

¹³C NMR (176 MHz, d⁶-DMSO): δ/ppm 112.5 (C4), 115.0 (C2), 143.0 (C3), 159.3 (C5), 160.4 (C1), 164.7 (C6).

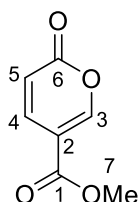
IR (neat) ν = 2958.0 (O-H, br w), 1699.8 (C=O, s), 1544.5 (m), 1404.5 (m), 1226.3 (C-O, s), 1130.1 (m), 1097.3 (C-O, s), 952.1 (m), 847.8 (m), 772.8 (s), 617.9 (m), 526.7 (m) cm⁻¹.

LC-MS: R_t = 0.92 min, *m/z* 138.9 [M-H]⁻.HR-MS calculated for C₆H₃O₄ at 139.0031, found 139.0020 (Δ = -7.9 ppm).

Decomposition by 150.0 °C (MeOH).

Reference¹

1.5 Methyl coumalate

Chemical Formula: C₇H₆O₄

Exact Mass: 154.03

Example procedure for the one-pot, two-step batch procedure from malic acid:

Malic acid (125.0 g, 933 mmol) was charged to a 1 L RBF fitted with a stirrer. Concentrated H₂SO₄ (250 mL, 4690 mmol) was slowly charged to the RBF, and the resulting slurry was heated to 90 °C for 3 h, during which time frothing was observed. The solution was cooled to RT, then lowered into an

ice bath. MeOH (160 mL, 3960 mmol) was charged dropwise over 15 mins. The solution was then heated at 90 °C for a further 2.5 h. The solution was allowed to cool to RT, then poured over ice and left overnight. Precipitation of the product was not observed. The orange solution was extracted with H₂O and DCM (100 mL x 3). The organic fractions were combined, and the volume reduced *in vacuo* to give the crude product as a yellow solid. Recrystallisation from EtOAc gave the product as a pale yellow solid in two crops, which were dried *in vacuo*.

Isolated yield: 38.26 g (124 mmol, 54%).

¹H NMR (700 MHz, CDCl₃): δ/ppm 3.87 (3 H, s, H7), 6.33 (1 H, dd, *J* = 9.8, 1.1 Hz, H2), 7.77 (1 H, dd, *J* = 9.8, 2.6 Hz, H3), 8.29 (1 H, dd, *J* = 2.6, 1.1 Hz, H5);

¹³C NMR (126 MHz, CDCl₃): δ/ppm 52.4 (C7), 111.9 (C4), 115.3 (C2), 141.6 (C3), 158.1 (C5), 159.8 (C1), 163.4 (C6).

IR (neat) ν = 1706.4 (C=O, s), 1544.8 (w), 1440.4 (m), 1298.8 (m), 1238.0 (s), 1084.6 (C-O, m), 948.1 (m), 839.1 (m), 815.6 (m), 773.2 (s), 630.0 (w) cm⁻¹.

LC-MS: *R*_t = 1.04 min, *m/z* 155.3 [MH]⁺.

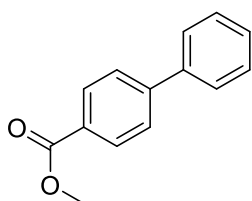
HR-MS calculated for C₇H₇O₄ at 155.0344, found 155.0347 (Δ = +1.9 ppm).

Melting point: 65.4-69.0 °C (EtOAc).

Reference²

1.6 Methyl 1,1'-biphenyl-4-carboxylate

Example preparation: Methyl coumalate (1.56 g, 10 mmol) and 1,3-diethynylbenzene (1.4 mL, 10 mmol) were charged to a 20 mL Biotage microwave vial fitted with a stirrer, followed by 1,4-dioxane (20 mL). The vial was capped, sealed and heated to 200 °C for 4 h with 5 mins pre-stirring in the microwave. The reaction mixture was transferred to a round bottom flask containing 10 g of silica and the solvent evaporated to dryness. The material was purified by column chromatography using 9:1 hexane:EtOAc.



Chemical Formula: C₁₄H₁₂O₂

Molecular Weight: 212.25

Isolated as a white solid in 93% yield following column chromatography (9:1 hexane:EtOAc).

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 – 8.01 (m, 2H), 7.85 – 7.79 (m, 2H), 7.76 – 7.71 (m, 2H), 7.54 – 7.47 (m, 2H), 7.46 – 7.40 (m, 1H), 3.88 (s, 3H).

¹³C NMR (101 MHz, DMSO) δ 166.50 (C), 145.13 (C), 139.27 (C), 130.26 (CH), 129.55 (CH), 128.89 (C), 128.86 (CH), 127.43 (CH), 127.40 (CH), 52.61 (CH₃).

IR (neat) ν = 1708.1 (s), 1604.9 (w), 1435.6 (m), 1404.1 (w), 1286.1 (s), 1267.6 (s), 1193.1 (m), 111.2 (s), 1003.2 (w), 961.1 (w), 857.0 (m), 744.6 (s), 699.4 (s), 688.3 (m) cm⁻¹.

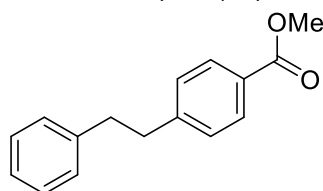
LC-MS: Rt = 2.95 m/z 213.5 (M+H).

HR-MS (ES+) calculated for C₁₄H₁₃O₂ at 213.0923, found 213.0916 (Δ = 3.3 ppm).

Melting point: 114.5-116.5 (EtOAc). Literature 117-118 °C (Methanol).⁹

Reference⁷

1.7 Methyl 4-(2-phenylethyl)benzoate



Chemical Formula: C₁₆H₁₆O₂
Molecular Weight: 240.30

Isolated as a clear liquid in 91% yield following column chromatography (9:1 hexane:EtOAc).

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 – 7.85 (m, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.13 (m, 5H), 3.83 (s, 3H), 2.91 (m, 4H).

¹³C NMR (101 MHz, DMSO) δ 166.63 (C), 147.75 (C), 141.52 (C), 129.60 (CH), 129.19 (CH), 128.80 (CH), 128.66 (CH), 127.79 (C), 126.34 (CH), 52.35 (CH₃), 37.41 (CH₂), 36.98 (CH₂).

IR (neat) ν = 1717.11 (s), 1620.5 (w), 1434.5 (m), 1275.2 (s), 1192.7 (w), 1178.3 (m), 1107.5 (m), 1020.1 (w), 754.0 (m), 697.1 (s), 521.7 (w) cm⁻¹.

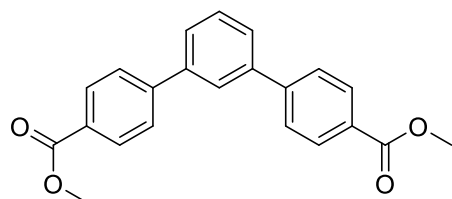
LC-MS: Rt = 3.19 m/z 242.0 (M+H).

HR-MS (ES+) calculated for C₁₆H₁₇O₂ at 241.1240, found 241.1229 (Δ = 4.6 ppm).

Reference⁸

1.8 Dimethyl 1,1':3',1''-terphenyl-4,4''-dicarboxylate

Procedure:^{3,4}



Chemical Formula: C₂₂H₁₈O₄
Molecular Weight: 346.38

Isolated as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.11 – 8.03 (m, 5H), 7.95 (d, *J* = 8.4 Hz, 4H), 7.79 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 3.89 (s, 6H).

¹³C NMR (101 MHz, DMSO) δ 166.51 (C), 144.85 (C), 140.16 (C), 130.36 (CH), 130.24 (CH), 129.13 (C), 127.74 (CH), 127.51 (CH), 126.13 (CH), 52.65 (CH₃).

IR (neat) ν = 1717.1 (s), 1520.1 (w), 1480.3 (w), 1279.8 (s), 1189.7 (m), 1107.0 (s), 758.6 (s), 699.5 (m) cm^{-1} .

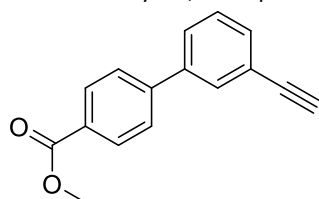
LC-MS: R_t = 3.60 m/z 347.2 (M+H).

HR-MS (ES+) calculated for $\text{C}_{22}\text{H}_{19}\text{O}_2$ at 347.1273, found 347.1283 (Δ = -2.9 ppm).

Melting point: 187.4-189.9 °C (EtOAc), literature = 192 °C (AcOH).

Reference⁵

1.9 Methyl 1,1'-biphenyl-3-ethynyl-4''-carboxylate



Chemical Formula: $\text{C}_{16}\text{H}_{12}\text{O}_2$
Molecular Weight: 236.27

Isolated as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.07 – 8.01 (m, 2H), 7.88 – 7.82 (m, 3H), 7.78 (dt, J = 6.7, 2.1 Hz, 1H), 7.58 – 7.47 (m, 2H), 4.29 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 166.42 (C), 143.96 (C), 139.74 (C), 132.00 (CH), 130.48 (CH), 130.27 (CH), 129.98 (CH), 129.29 (C), 128.08 (CH), 127.55 (CH), 123.05 (C), 83.64 (C), 81.73 (CH), 52.64 (CH_3).

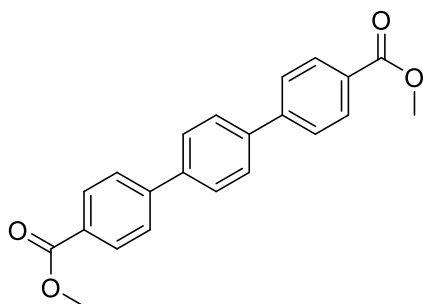
IR (neat) ν = 3260.7 (m), 1707.3 (s), 1604.4 (w), 1430.6 (m), 1276.8 (s), 1196.4 (m), 1111.0 (s), 1014.9 (w), 956.8 (w), 858.8 (m), 801.5 (s), 765.8 (s), 699.2 (s), 671.6 (s), 606.1 (s) cm^{-1} .

LC-MS: R_t = 3.02 m/z 237.2 (M+H).

HR-MS (ES+) calculated for $\text{C}_{16}\text{H}_{13}\text{O}_2$ at 237.0920, found 237.0916 (Δ = 1.7 ppm).

Melting point: 109.0-110.2 °C.

1.10 Dimethyl 1,1':4',1''-terphenyl-4,4''-dicarboxylate



Chemical Formula: $\text{C}_{22}\text{H}_{18}\text{O}_4$
Molecular Weight: 346.38

Isolated as a white solid.

RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives

^1H NMR (700 MHz, d_6 -DMSO): δ /ppm 8.09 – 7.97 (m, 4H), 7.93 – 7.82 (m, 6H), 3.86 (s, 3H), 3.54 (s, 3H).

^{13}C NMR (175 MHz, d_6 -DMSO) δ /ppm 167.52 (C), 166.47 (C), 144.32 (C), 139.31 (C), 130.45 (CH), 130.30 (CH), 128.08 (CH), 128.07 (CH), 127.35 (CH), 127.20 (CH), 66.79 (CH₃), 52.63 (CH₃).

IR (neat) ν = 1718.2 (s), 1431.8 (m), 1398.5 (m), 1297.5 (m), 1274.2 (s), 1193.2 (s), 1109.1 (s), 1016.3 (w), 952.9 (w), 828.3 (s), 760.9 (s), 693.7 (m) cm^{-1} .

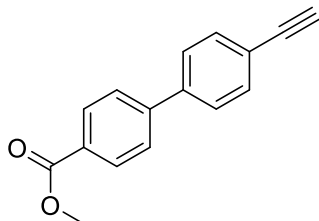
LC-MS: R_t = 3.43 m/z 347.4 (M+H).

HR-MS (ES+) calculated for C₂₂H₁₉O₂ at 347.1290, found 347.1283 (Δ = 2.0 ppm).

Melting point: >250 °C.

Reference⁶

1.11 Methyl 1,1'-biphenyl-4-ethynyl-4''-carboxylate



Chemical Formula: C₁₆H₁₂O₂

Molecular Weight: 236.27

Isolated as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 8.09 – 7.97 (m, 2H), 7.90 – 7.83 (m, 2H), 7.82 – 7.73 (m, 2H), 7.66 – 7.55 (m, 2H), 4.32 (s, 1H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 166.41 (C), 143.99 (C), 139.54 (C), 132.86 (CH), 130.31 (CH), 129.28 (C), 127.66 (CH), 127.45 (CH), 122.19 (C), 83.60 (C), 82.50 (CH), 52.66 (CH₃).

IR (neat) ν = 3257.5 (m), 1710.3 (s), 1600.7 (w), 1434.6 (m), 1399.4 (m), 1295.0 (s), 1283.7 (s), 1270.5 (s), 1220.7 (m), 1191.7 (m), 1112.6 (s), 1017.9 (w), 1002.8 (w), 953.7 (w), 832.0 (s), 770.9 (s), 696.8 (m) cm^{-1} .

LC-MS: R_t = 3.05 m/z 237.2 (M+H).

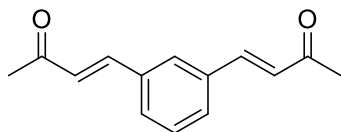
HR-MS (ES+) calculated for C₁₆H₁₄O₂ at 237.0925, found 237.0916 (Δ = 3.8 ppm).

Melting point: 149.6-151.2 °C.

Reference¹⁰

1.12 (3*E*,3'*E*)-3,4'-(1,3-Phenylene)*bis*(but-3-en-2-one)

Synthesised following the literature procedure:¹¹



Chemical Formula: C₁₄H₁₄O₂

Molecular Weight: 214.26

Pale yellow solid, isolated in 80% yield on a 500 mmol scale.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 1.9 Hz, 1H), 7.59 – 7.46 (m, 4H), 7.46 – 7.39 (m, 1H), 6.74 (dd, *J* = 16.3, 1.8 Hz, 2H), 2.38 (d, *J* = 1.3 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 198.01 (C), 142.23 (CH), 135.23(C), 129.82 (CH), 129.61 (CH), 127.96 (CH), 127.90 (CH), 27.71 (CH₃).

IR (neat) ν = 1671.7 (m), 1647.6 (s), 1619.5 (m), 1357.9 (m), 1332.3 (w), 1297.7 (w), 1264.0 (s), 1241.1 (s), 1162.4 (w), 980.6 (s), 784.0 (s), 690.6 (m), 566.7 (s) cm⁻¹.

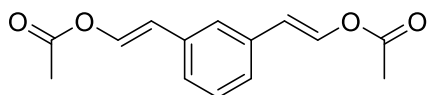
EI GC non polar compounds Rt 5.53 m/z 214.1.

Melting point: 100.8-102.0 °C.

Reference:¹³

1.13 (1*E*,1'*E*)-(1,3-phenylene)*bis*(ethene-2,1-diyl) diacetate

Synthesised following the literature procedure:¹²



Chemical Formula: C₁₄H₁₄O₄

Molecular Weight: 246.2620

White solid, isolated in 64% yield on a 50 mmol scale.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 12.8 Hz, 2H), 7.37 – 7.14 (m, 4H), 6.39 (d, *J* = 12.8 Hz, 2H), 2.22 (s, 6H).

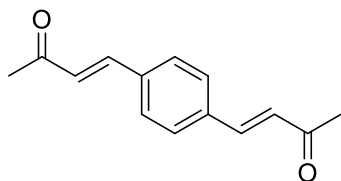
¹³C NMR (101 MHz, CDCl₃) δ 167.96 (C), 136.51 (CH), 134.60 (C), 129.06 (CH), 125.16 (CH), 124.19 (CH), 114.93 (CH), 20.74 (CH₃).

IR (neat) ν = 1735.5 (m), 1656.3 (w), 1364.1 (m), 1217.6 (s), 1119.0 (m), 1081.3 (s), 1049.1 (m), 931.6 (s), 793.4 (m), 650.1 (m), 598.3 (m), 540.9 (m) cm⁻¹.

Melting point: 72.5.0-74.4 °C.

1.14 (3*E*,3'*E*)-4,4'-(1,4-Phenylene)*bis*(but-3-en-2-one)

Synthesised following the literature procedure:¹¹



Chemical Formula: C₁₄H₁₄O₂

Molecular Weight: 214.26

Pale yellow solid, isolated in 83% yield on a 500 mmol scale.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.56 (m, 4H), 7.50 (d, *J* = 16.2 Hz, 2H), 6.76 (dt, *J* = 16.2, 0.8 Hz, 2H), 2.40 (d, *J* = 0.8 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 198.06 (C), 142.03 (CH), 136.41 (C), 128.76 (CH), 128.00 (CH), 27.72 (CH₃).

IR (neat) ν = 1662.0 (s), 1639.8 (s), 1622.7 (m), 1413.6 (w), 1357.8 (m), 1413.6 (w), 1325.0 (w), 1256.3 (m), 1200.1 (w), 1010.5 (w), 981.2 (s), 971.1 (s), 877.7 (w), 809.2 (s), 802.0 (s), 589.1 (w), 559.7 (m), 497.6 (m) cm⁻¹.

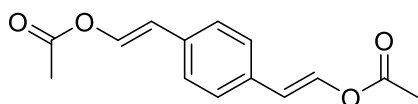
El GC non polar compounds Rt 5.59 m/z 214.1.

Melting point: 149.3-152.0 °C.

Reference:¹⁴

1.15 (1*E*,1'*E*)-1,4-(phenylene)*bis*(ethene-2,1-diyl) diacetate

Synthesised following the literature procedure:¹²



Chemical Formula: C₁₄H₁₄O₄

Molecular Weight: 246.2620

White solid, isolated in 83% yield on a 50 mmol scale.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 12.8 Hz, 2H), 7.29 (s, 4H), 6.38 (d, *J* = 12.8 Hz, 2H), 2.21 (s, 6H).

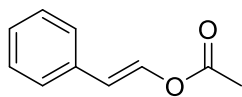
¹³C NMR (101 MHz, CDCl₃) δ 167.93 (C), 136.21 (CH), 133.27 (C), 126.52 (CH), 114.86 (CH), 20.73 (CH₃).

IR (neat) ν = 1745.5 (s), 1431.2 (m), 1209.8 (s), 1176.0 (m), 1110.1 (m), 1084.3 (s), 1043.3 (m), 949.7 (s), 926.1 (s), 891.4 (m), 786.3 (m), 692.19 (s) cm⁻¹.

Melting point: 149.3-151.3 °C.

1.16 (*E*)-2-Phenylvinyl acetate

Synthesised following the literature procedure:¹²



Chemical Formula: C₁₀H₁₀O₂

Molecular Weight: 162.1880

Small residual ethyl acetate signals are present in the spectra, and despite high vacuum drying for 48 h this could not be removed.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 12.8 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.30 – 7.21 (m, 1H), 6.43 (d, *J* = 12.8 Hz, 1H), 2.22 (s, 3H).

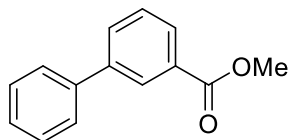
¹³C NMR (101 MHz, CDCl₃) δ 168.00 (C), 136.24 (CH), 134.13 (C), 128.72 (CH), 127.43 (CH), 126.23 (CH), 115.28 (CH), 20.74 (CH₃).

IR (neat) ν = 1754.9 (s), 1661.7 (w), 1369.7 (m), 1209.1 (s), 1199.4 (s), 1093.9 (s), 1070.3 (m), 929.0 (s), 820.9 (w), 749.8 (s), 691.9 (s), 650.6 (m), 594.4 (m), 509.3 (m) cm⁻¹.

LC (MeCN) Rt 2.47 m/z 163.1.

HR-MS (ES⁺) calculated for C₁₀H₁₁O₂ at 163.0759, found 163.0768 (Δ = 5.5 ppm (0.9 mDa)).

1.17 Methyl 1,1'-biphenyl-3-carboxylate



Chemical Formula: C₁₄H₁₂O₂

Molecular Weight: 212.2480

β-Methoxystyrene; CAS 4747-15-3, was purchased from Sigma Aldrich chemicals as a mixture of *cis* and *trans* isomers, technical grade, 90% and was used as supplied.

¹H NMR (400 MHz, Chloroform-*d*) δ 8.33 (t, *J* = 1.7 Hz, 1H), 8.06 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.66 (dt, *J* = 8.1, 1 Hz, 2H), 7.58 – 7.46 (m, 3H), 7.44 – 7.37 (m, 1H), 3.98 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 167.05 (C), 141.48 (C), 140.12 (C), 131.54 (CH), 130.71 (C), 128.91 (CH), 128.87 (CH), 128.36 (CH), 128.28 (CH), 127.76 (CH), 127.17 (CH), 52.20 (CH₃).

IR (neat) ν = 1718.2 (s), 1454.2 (w), 1435.3 (m), 1299.6 (s), 1239.0 (s), 1110.0 (m), 1088.7 (w), 1049.0 (w), 739.2 (s), 694.5 (s), 671.4 (w), 614.3 (w) cm⁻¹.

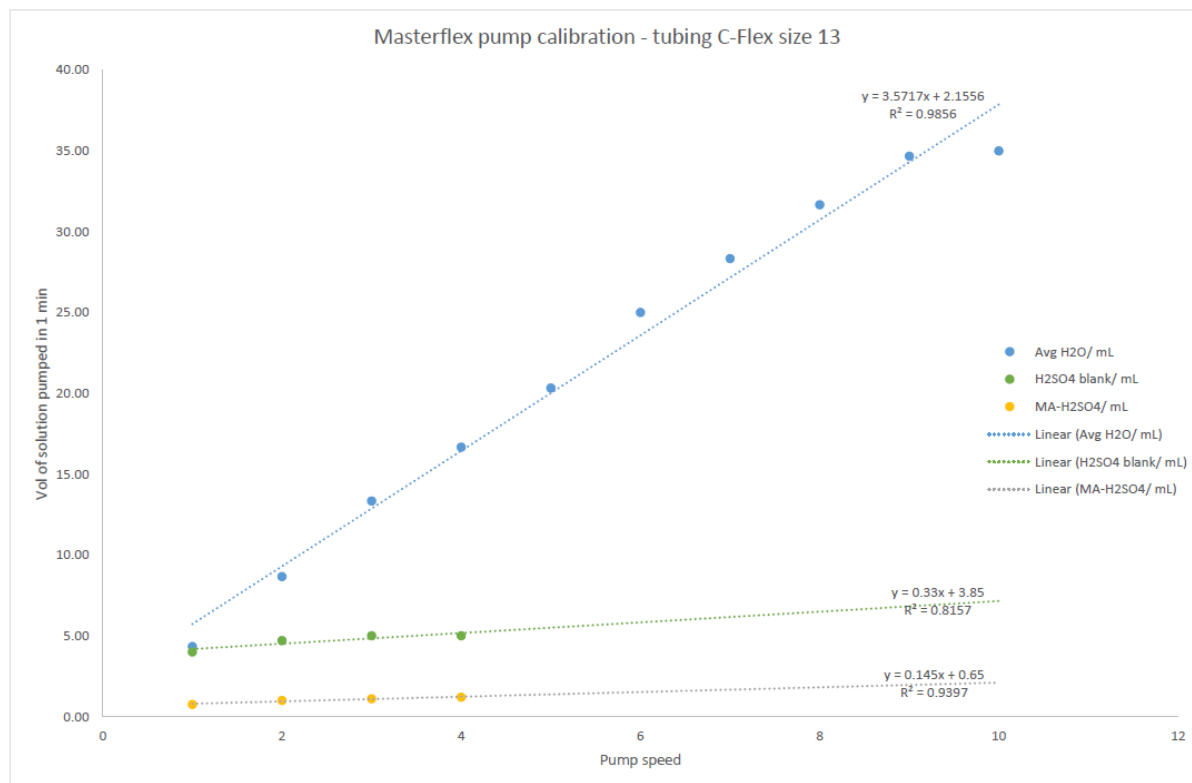
LC (MeCN) Rt 3.26 m/z 213.2.

HR-MS (ES⁺) calculated for C₁₄H₁₃O₂ at 213.0916, found 213.0905 (Δ = -5.2 ppm (-1.1 mDa)).

Reference:¹⁵

2 Calibration data

Calibration of the Masterflex pump was performed with H₂O, conc. H₂SO₄ and the stock solution of malic acid-H₂SO₄. Adding malic acid to the conc. sulfuric acid increased the viscosity even further. It was not possible to operate the pump above a speed of '4'. A pump speed of '2' was used in future reactions, which gave a typical flow rate of around 0.8 mL min⁻¹.



3 Calculations and statistical analysis

3.1 Calculation of conversion

The stoichiometry of the reaction gives the following equation which was used to calculate the % conversion, where CA = the integral of the peak at $\delta = 7.77$ ppm, and MA = the integral of the peak at $\delta = 4.26$ ppm.

$$\% \text{ Conversion} = \frac{2CA}{MA + 2CA}$$

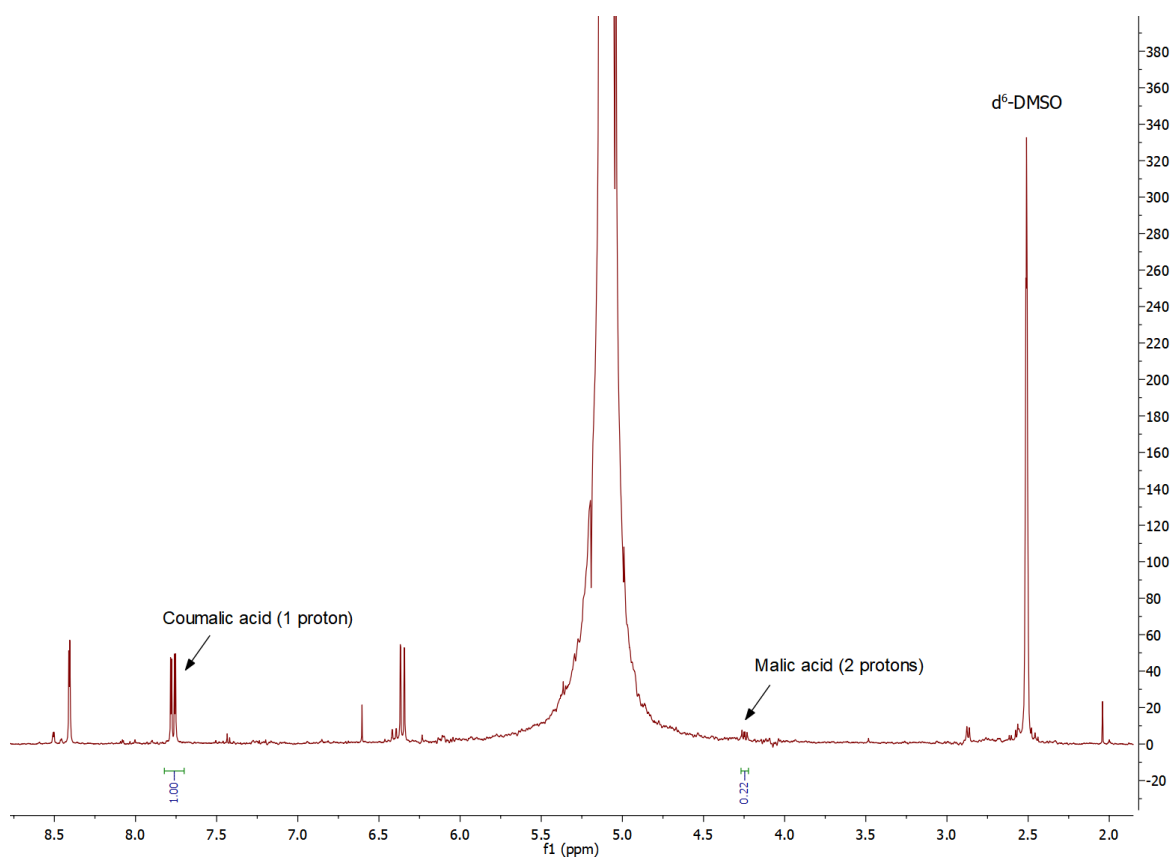


Figure S3 – Example ^1H NMR spectrum showing coumalic acid, malic acid, solvent and acid.

3.2 Calculation of throughput and space-time yield

The throughput is given by:

$$\text{Throughput} = \frac{\text{mass produced (g)}}{\text{time taken (h)}}$$

The space-time yield is given by:

$$\text{Space – time yield} = \frac{\text{mass (kg)}}{\text{reactor volume (m}^3\text{)} \cdot \text{time(h)}}$$

Batch process; See batch process page 6 200g scale.

The throughput is calculated by:

$$\text{Throughput} = \frac{51 \text{ g}}{6 \text{ h}} = 8.5 \text{ g h}^{-1}$$

The reactor volume is the size of the round-bottomed flask used in the reaction (1 L). Thus, the space-time yield is:

$$\text{Space – time yield} = \frac{0.051 \text{ kg}}{1 \times 10^{-3} \text{ m}^3 \cdot 6 \text{ h}} = 8.5 \text{ kg m}^{-3} \text{ h}^{-1}$$

Vapourtec process (in-built pump).

The throughput was calculated as:

$$\text{Throughput} = \frac{5.1 \text{ g}}{1.17 \text{ h}} = 4.4 \text{ g h}^{-1}$$

The reactor volume was assumed to be the volume of the two reactor coils plus the volume of the connecting tubing, giving a total of 25 mL. Thus, the space-time yield is given by:

$$\text{Space - time yield} = \frac{0.0051 \text{ kg}}{25 \times 10^{-6} \text{ m}^3 \cdot 1.17 \text{ h}} = 174.4 \text{ kg m}^{-3} \text{ h}^{-1}$$

HeRo process

Several assumptions have been made to enable calculation of the reactor volume of the HeRo reactor. These are:

- The solution is homogeneous. This is known to be inaccurate, because significant gas production is observed during the reaction.
- The film thickness is constant at 2 mm.
- The rivulet width is constant at 5 mm.
- Only a single helix is produced.
- The number of turns in the helix is 15.
- The rise of the helix in one revolution is 40 mm.
- Helical behaviour is observed for the full 600 mm of the work-tube.

The rivulet has been treated as though it is a ribbon which can be unfurled to give a cuboid (dimensions: path length x 2 mm x 5 mm). The radius of the path length can be found *via* the following calculation:

$$\begin{aligned} \text{Path length, } D &= N\sqrt{H^2 + (2\pi r)^2} + (600 - L_h) \\ D &= 15\sqrt{(40^2) + (36\pi)^2} = 1.8 \text{ m} \end{aligned}$$

Therefore the volume of the rivulet (and thus the volume of the reactor) is:

$$\text{Volume} = 1.8 \text{ m} \cdot 2 \times 10^{-3} \text{ m} \cdot 5 \times 10^{-3} \text{ m} = 1.8 \times 10^{-5} \text{ m}^3$$

Thus, the space-time yield of the HeRo process, calculated from the 8 h experiment is found by the following calculation:

$$\text{Space - time yield} = \frac{0.2857 \text{ kg}}{1.8 \times 10^{-5} \text{ m}^3 \cdot 8 \text{ h}} = 1980 \text{ kg m}^{-3} \text{ h}^{-1}$$

This is more than 3.5 times than the space-time yield of the Vapourtec process, and approx. 36 times the space-time yield of the most efficient batch process.

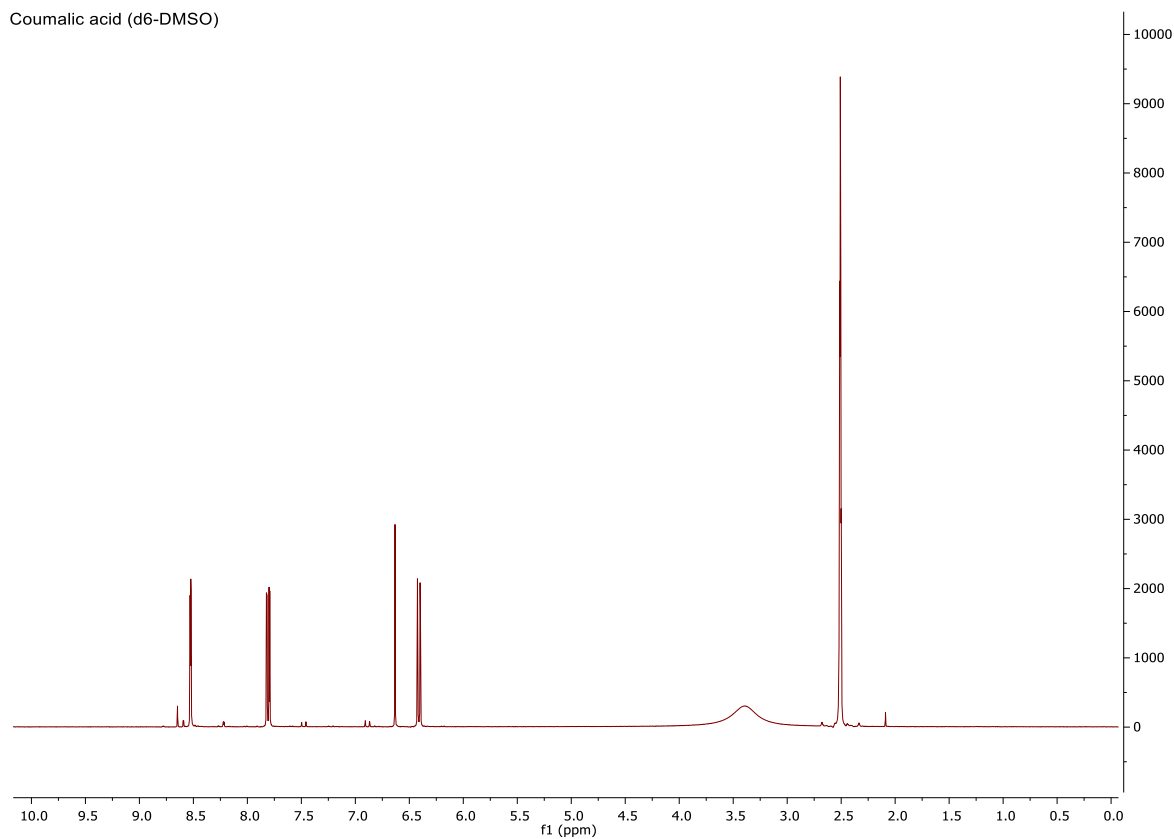
Alternatively using a more conventional calculation based upon the total volume of the glass processing tube yields a modified value of:

$$\text{Space - time yield} = \frac{0.2857 \text{ kg}}{1.94 \times 10^{-4} \text{ m}^3 \cdot 8 \text{ h}} = 184.1 \text{ kg m}^{-3} \text{ h}^{-1}$$

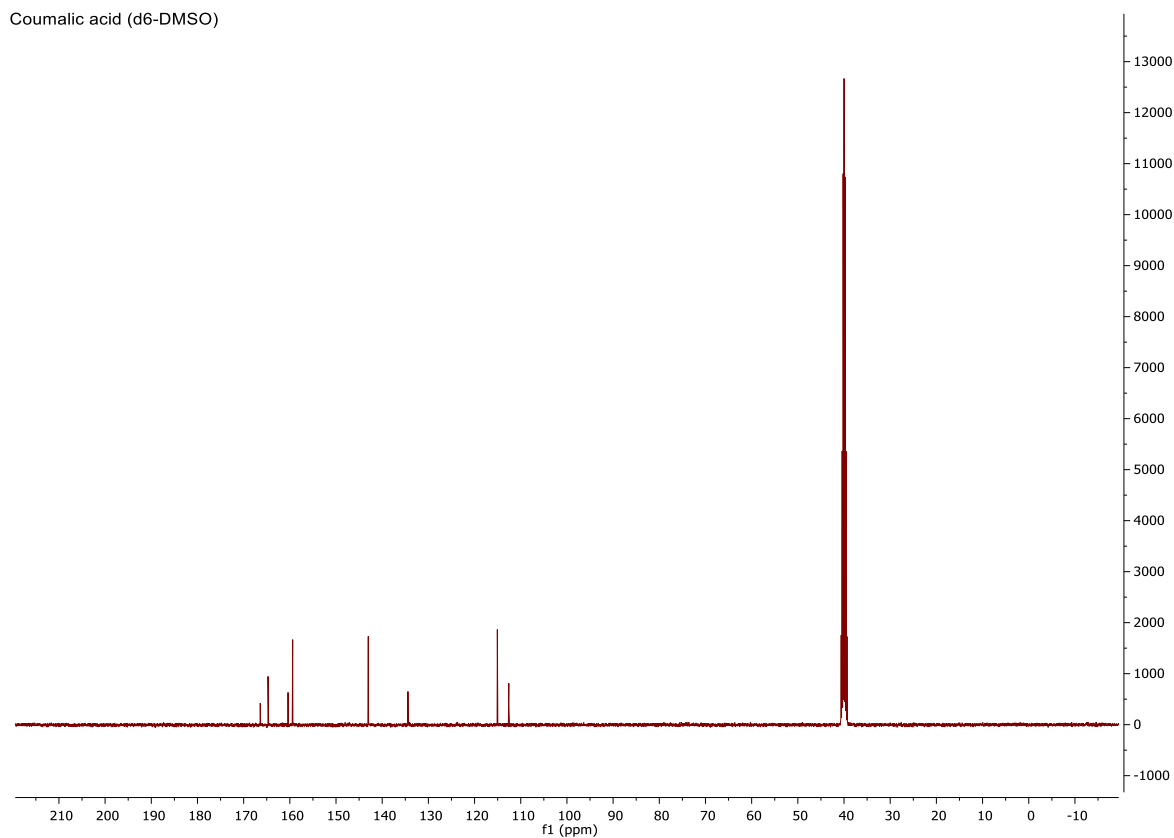
4 Spectral data

4.1 Coumalic acid

Coumalic acid (d6-DMSO)

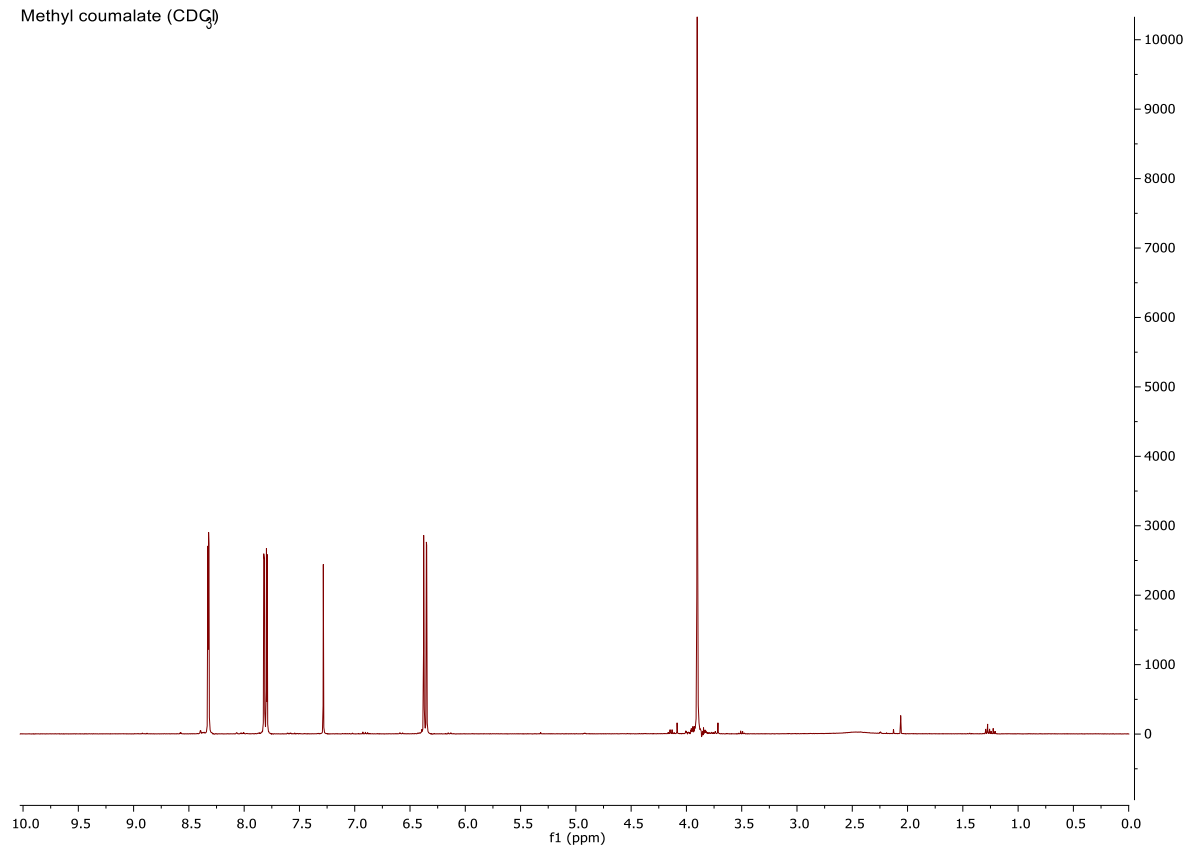


Coumalic acid (d6-DMSO)

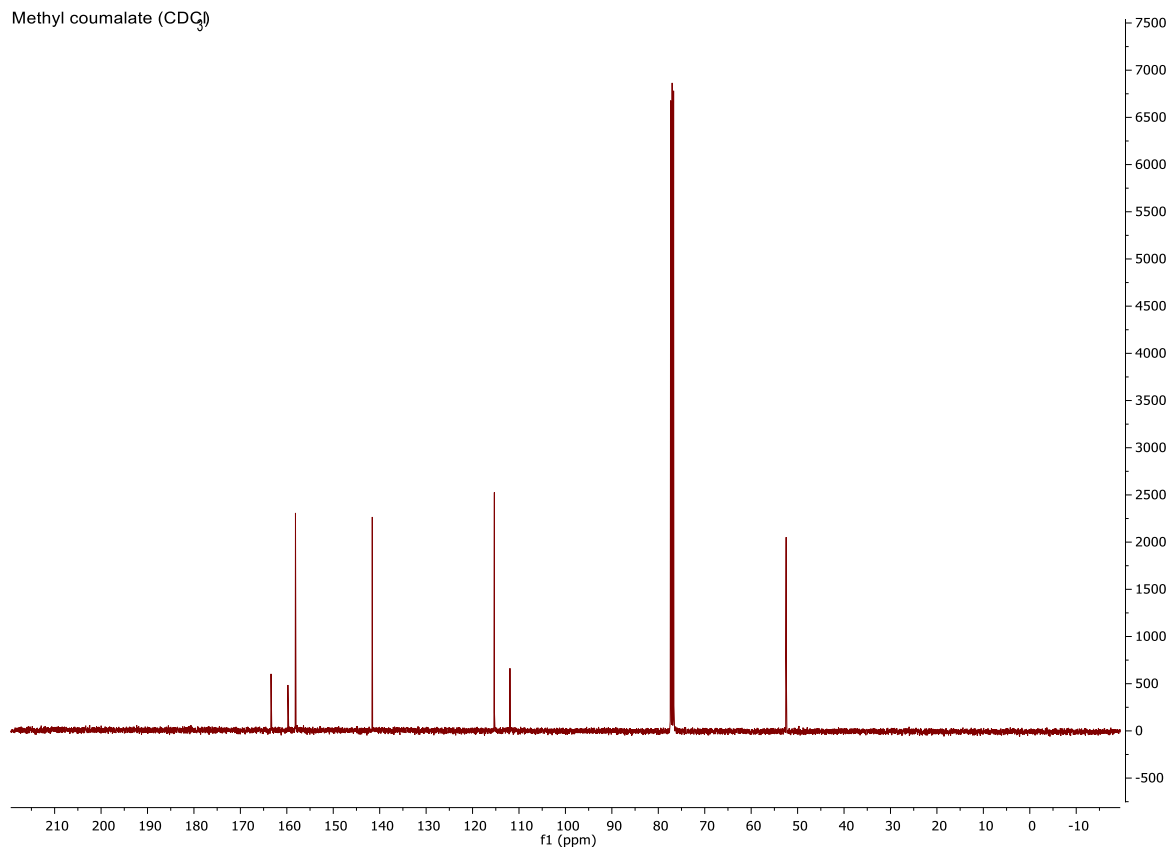


4.2 Methyl coumalate

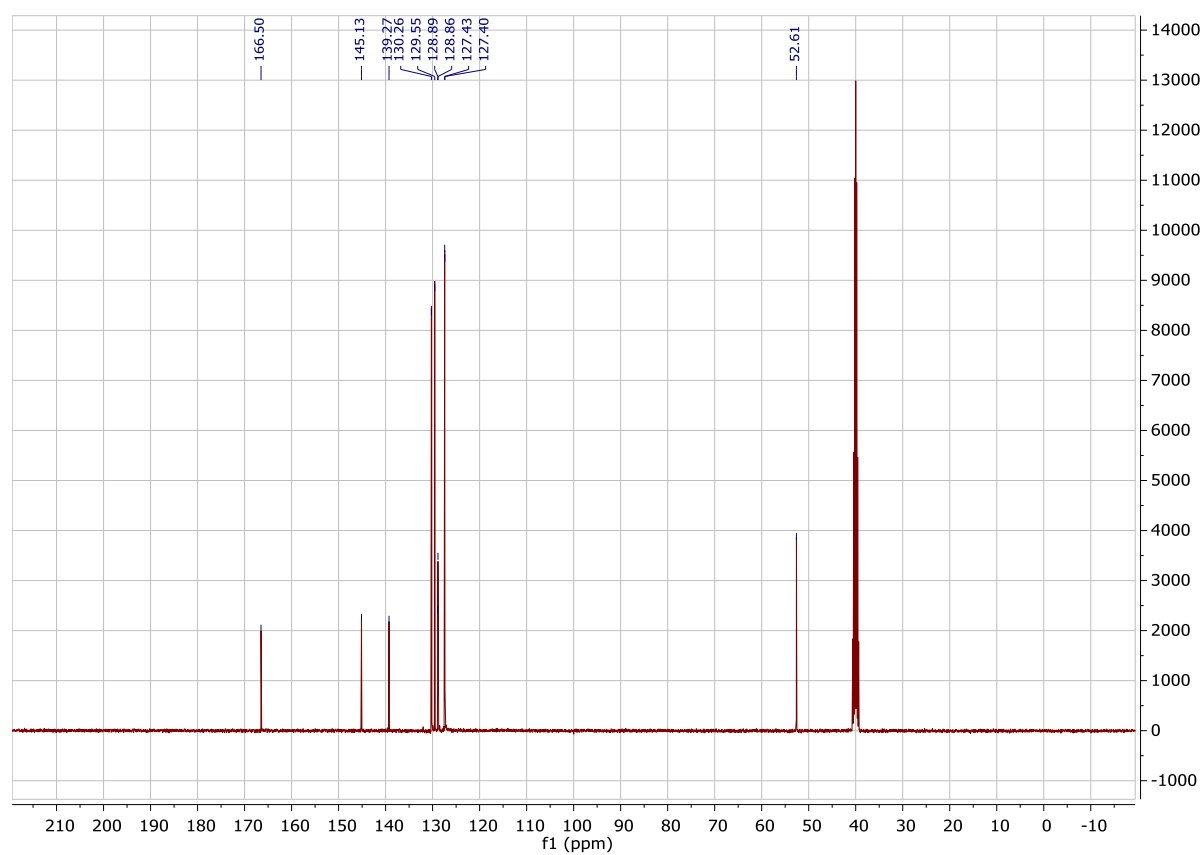
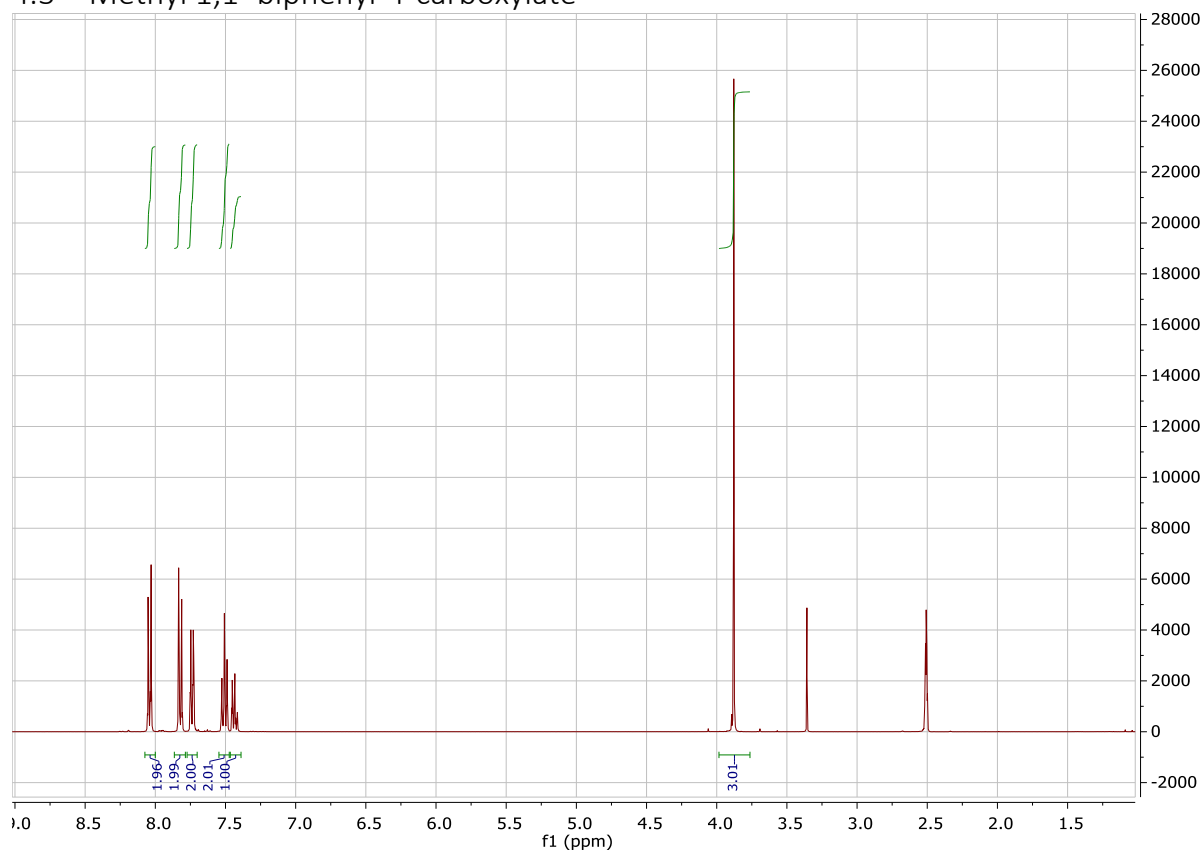
Methyl coumalate (CDCl₃)



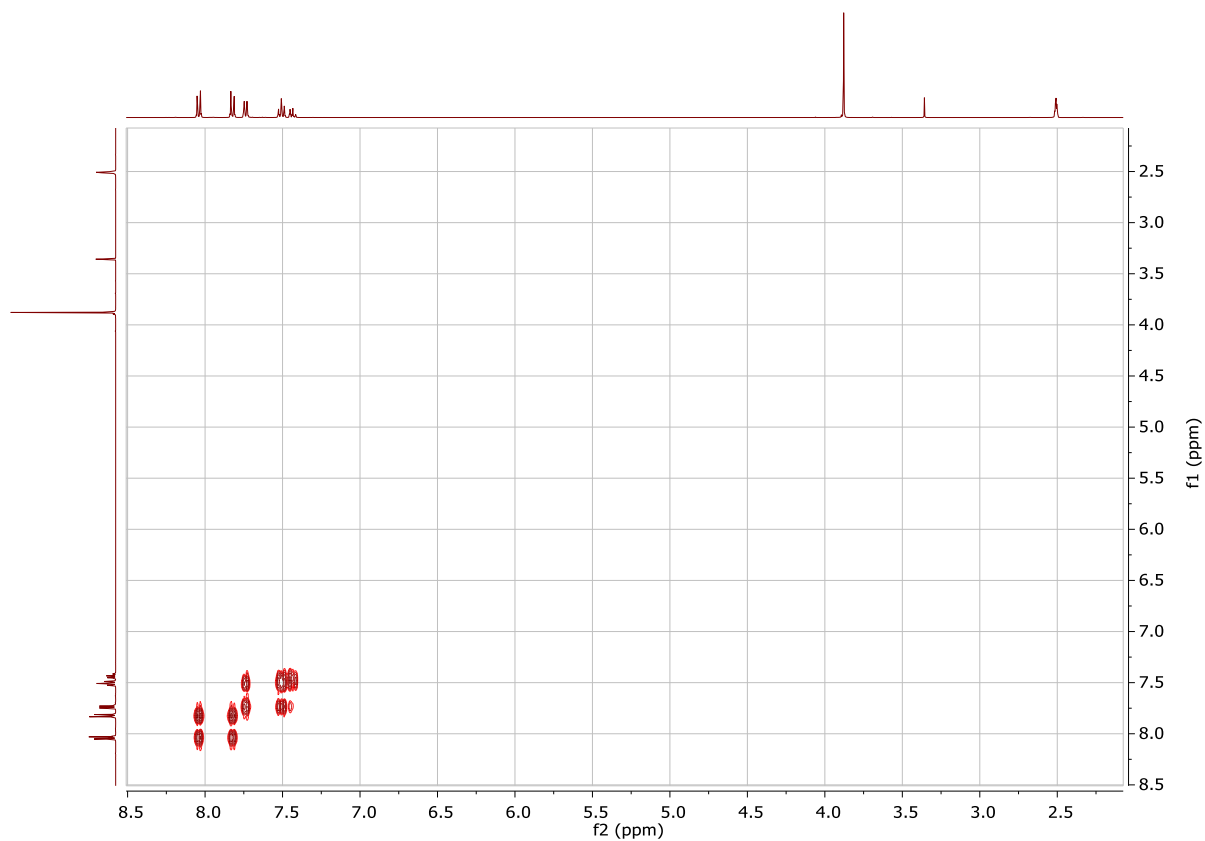
Methyl coumalate (CDCl₃)



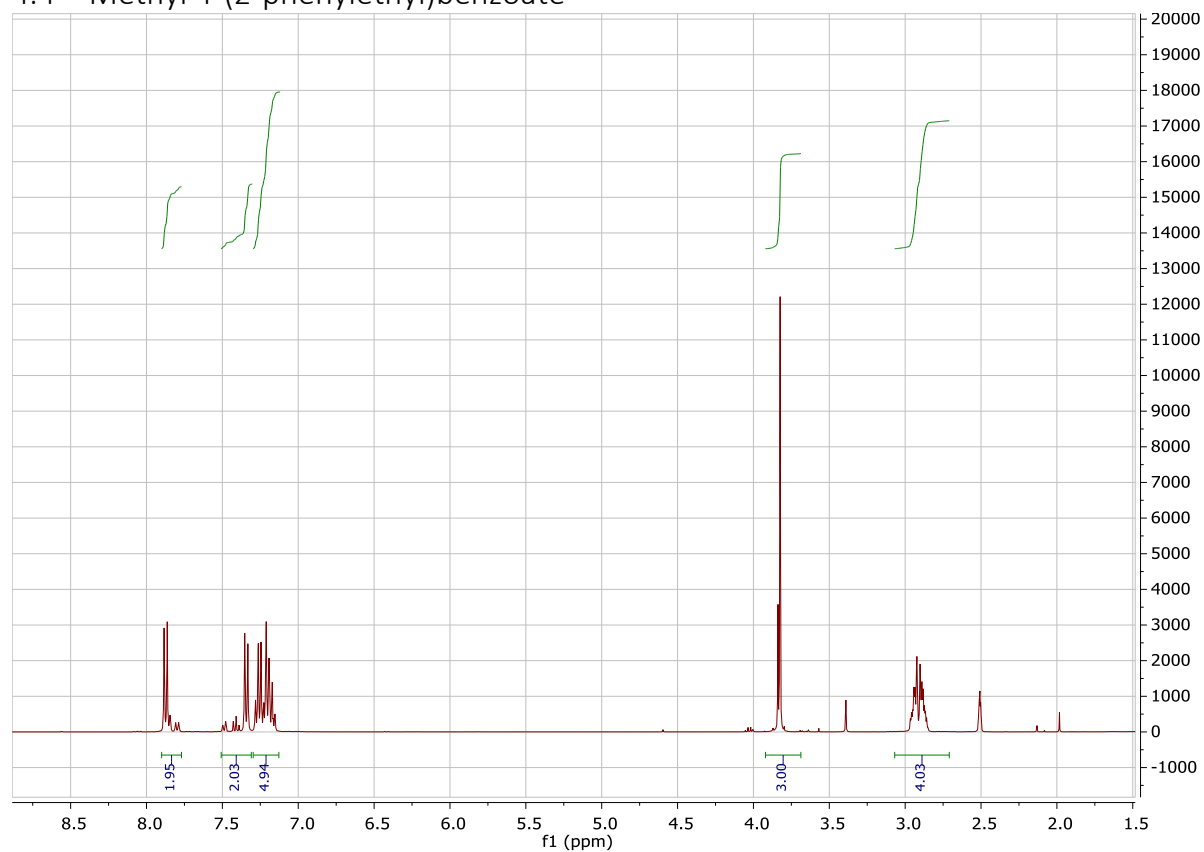
4.3 Methyl 1,1'-biphenyl-4-carboxylate



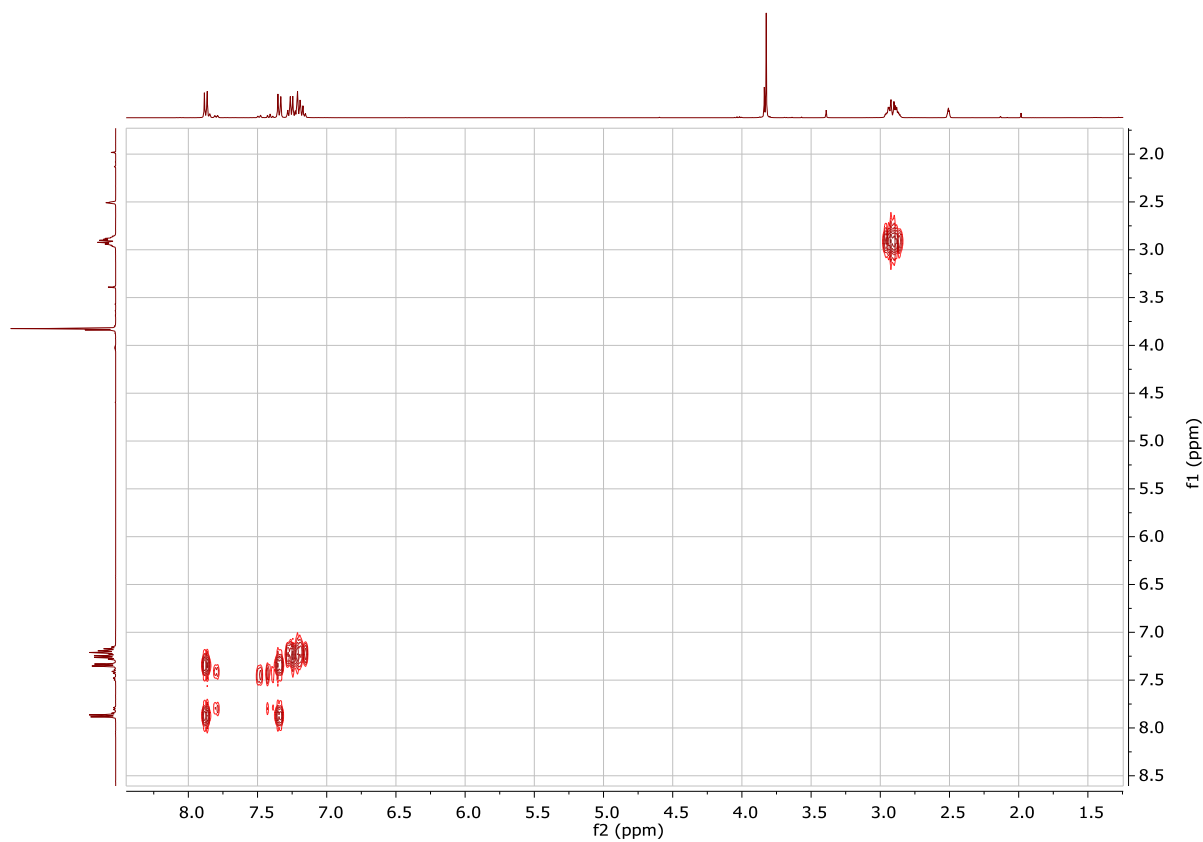
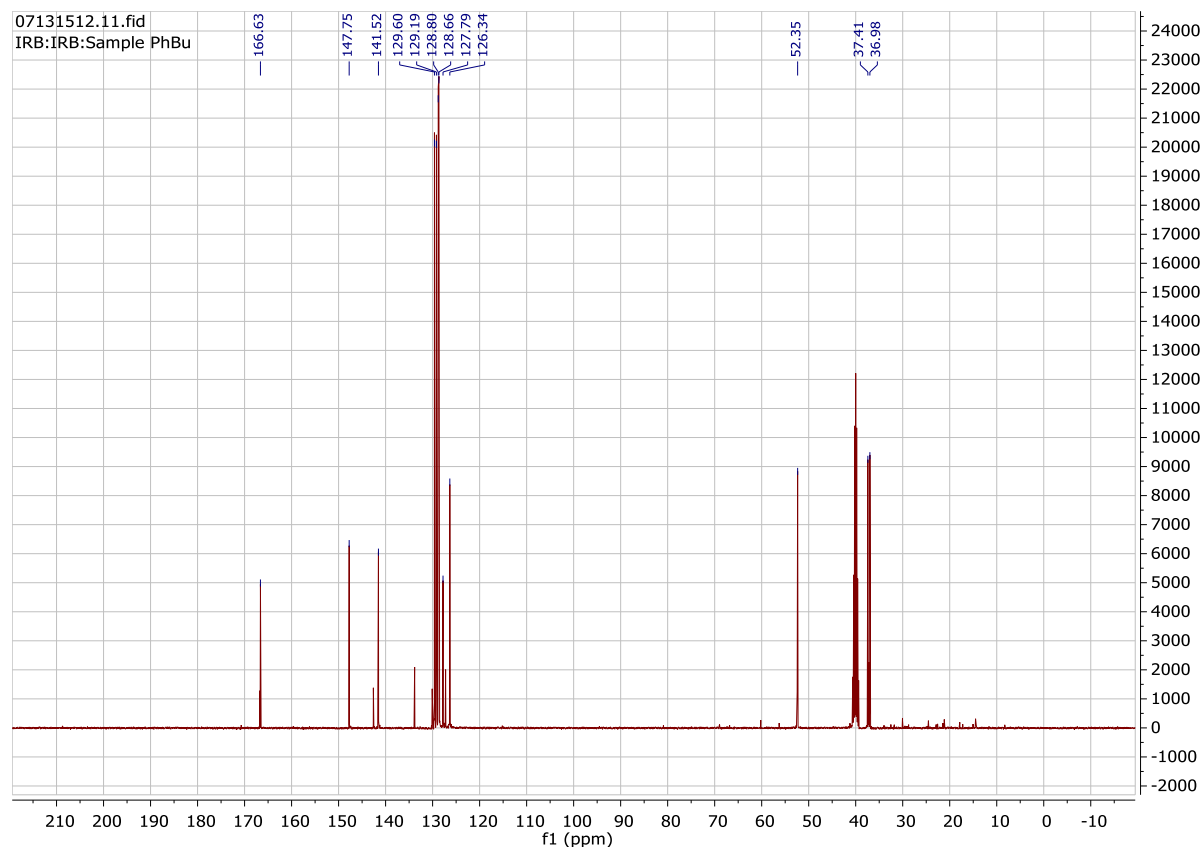
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



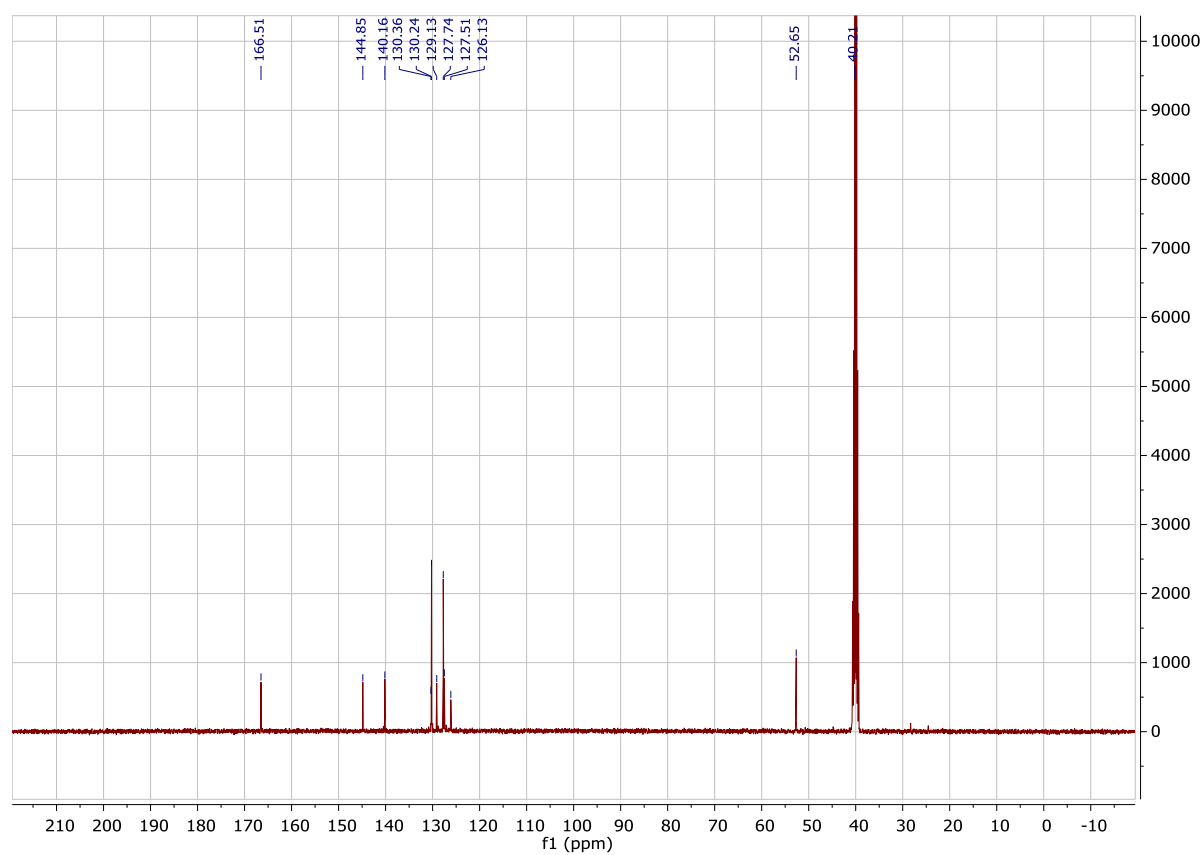
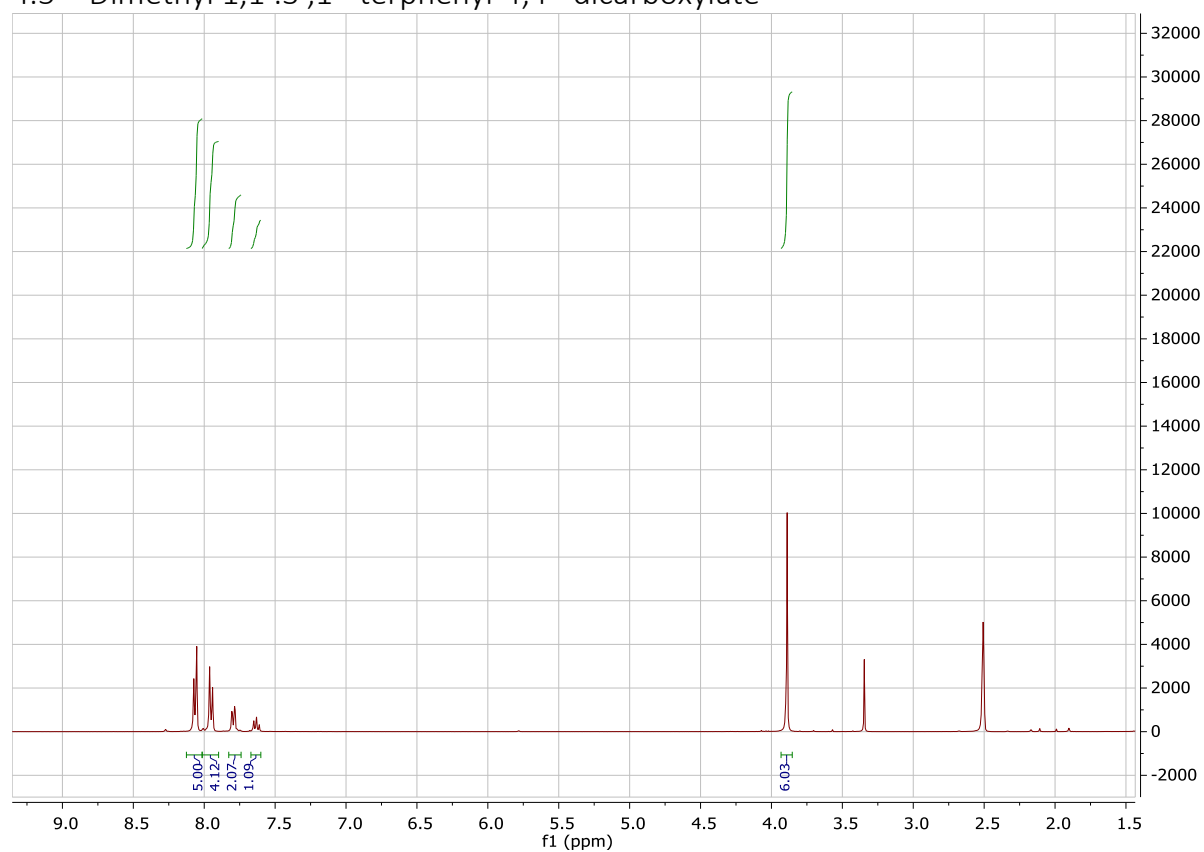
4.4 Methyl 4-(2-phenylethyl)benzoate



RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



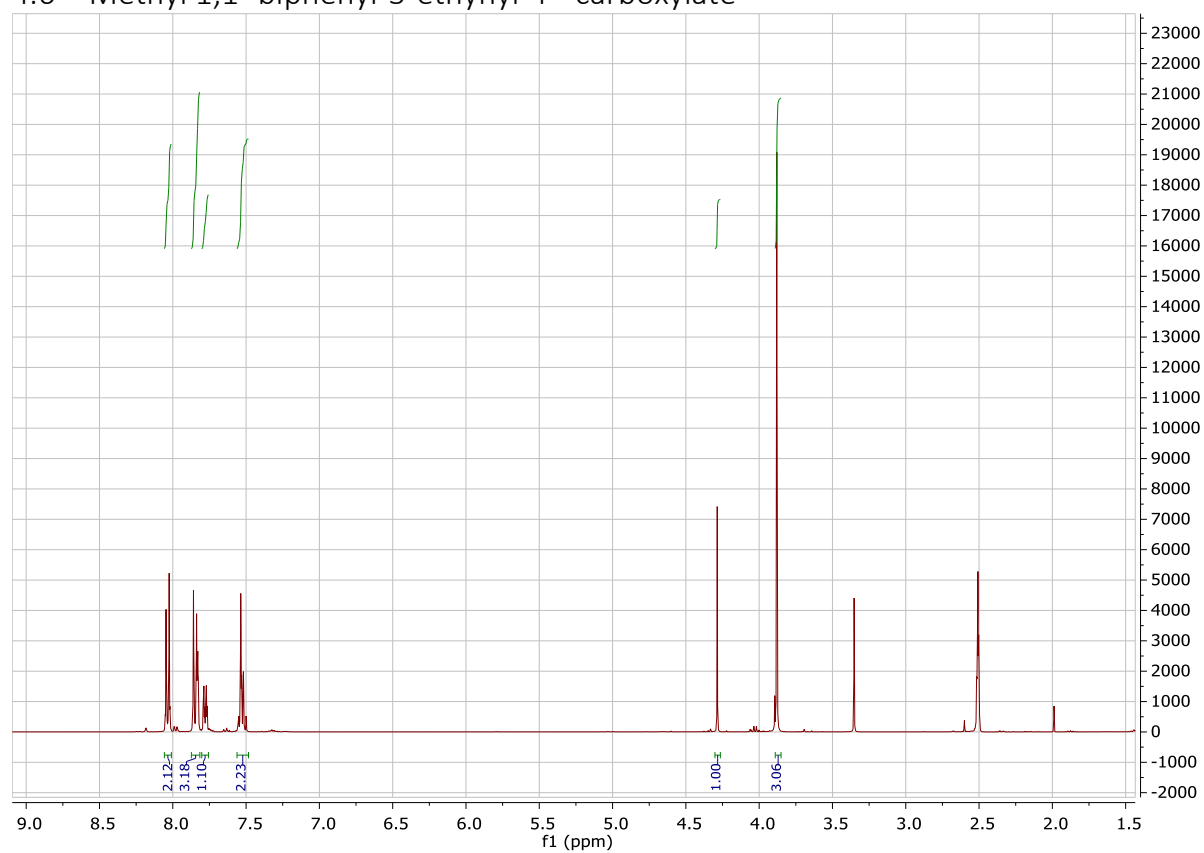
4.5 Dimethyl 1,1':3',1''-terphenyl-4,4''-dicarboxylate



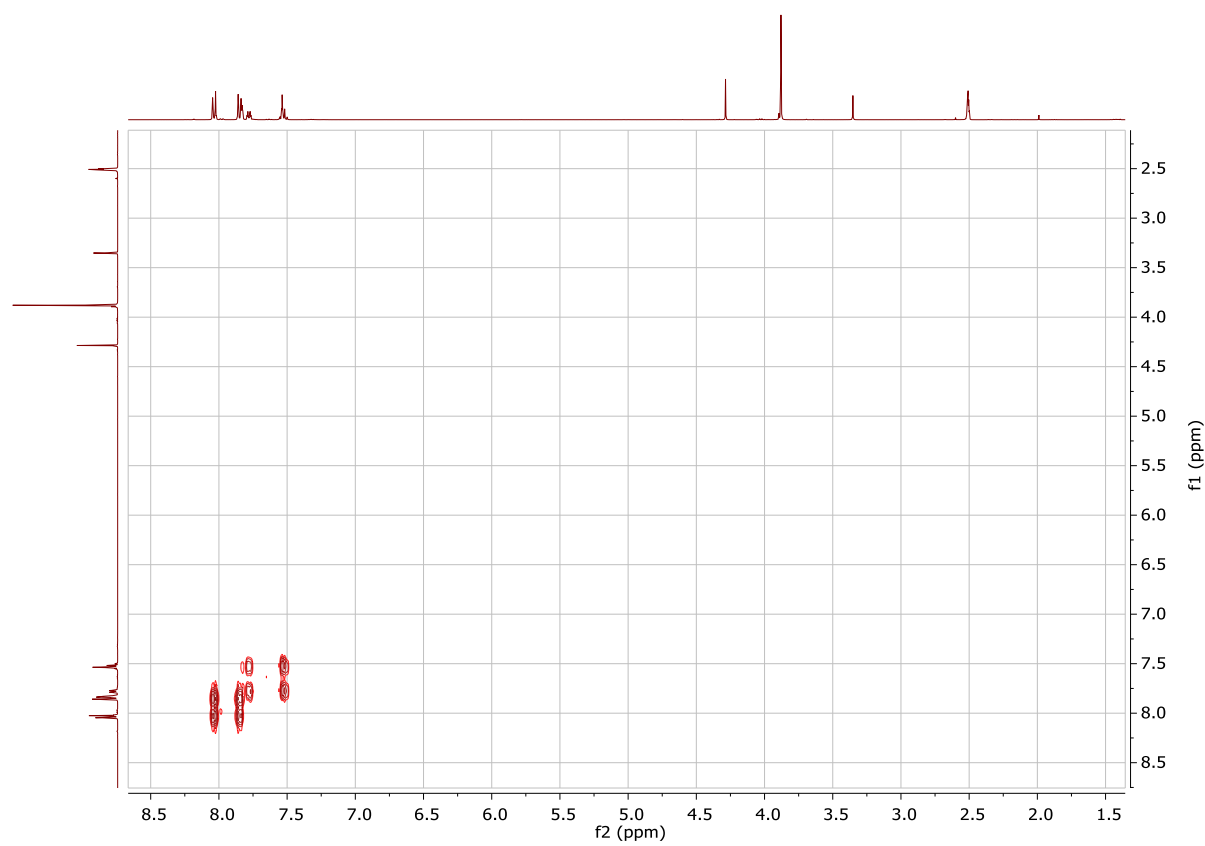
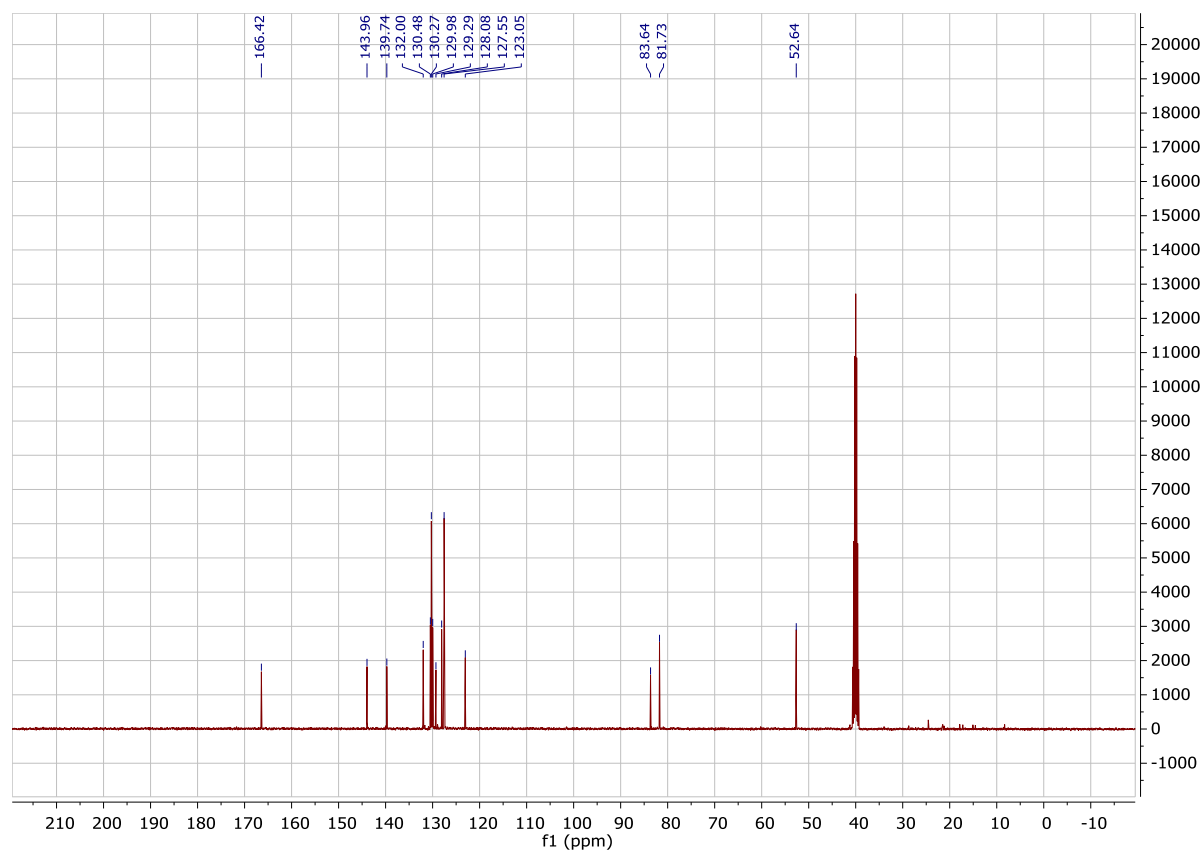
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



4.6 Methyl 1,1'-biphenyl-3-ethynyl-4''-carboxylate

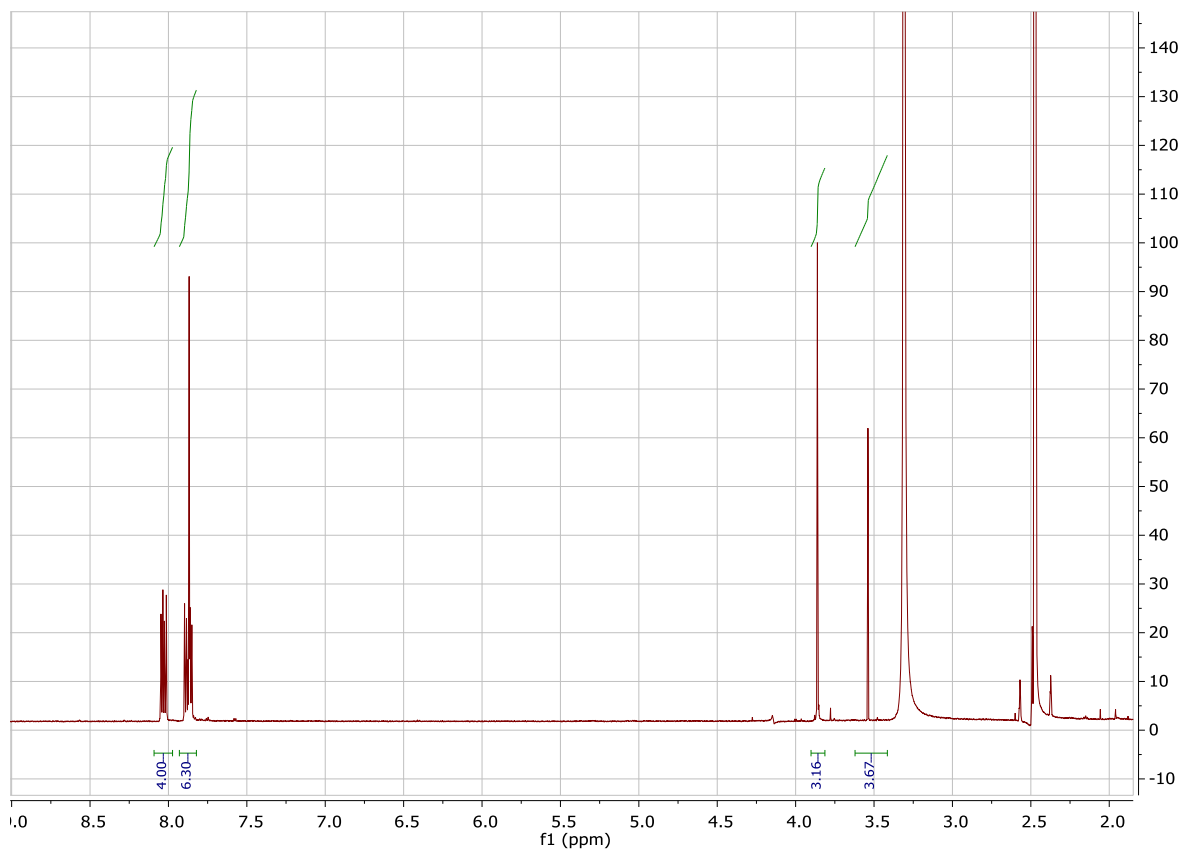


RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives

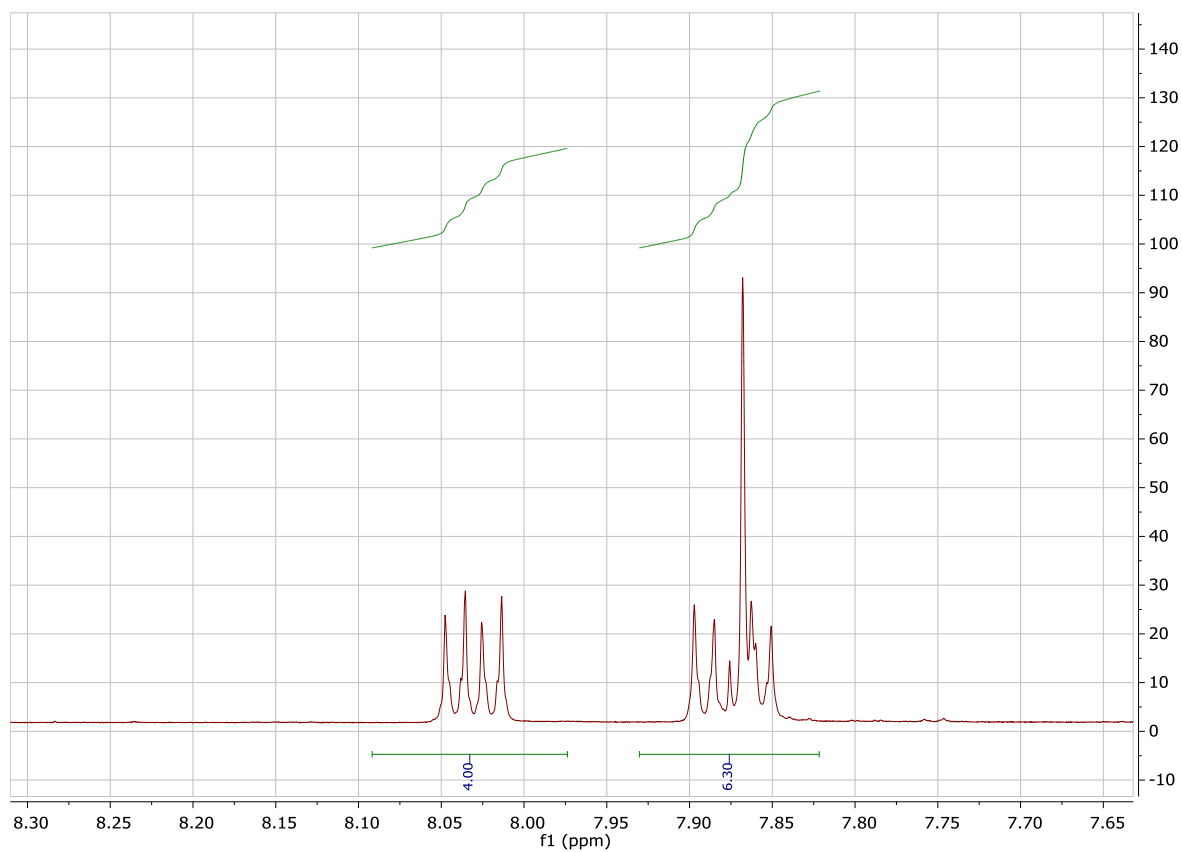


4.7 Dimethyl 1,1':4',1''-terphenyl-4,4''-dicarboxylate

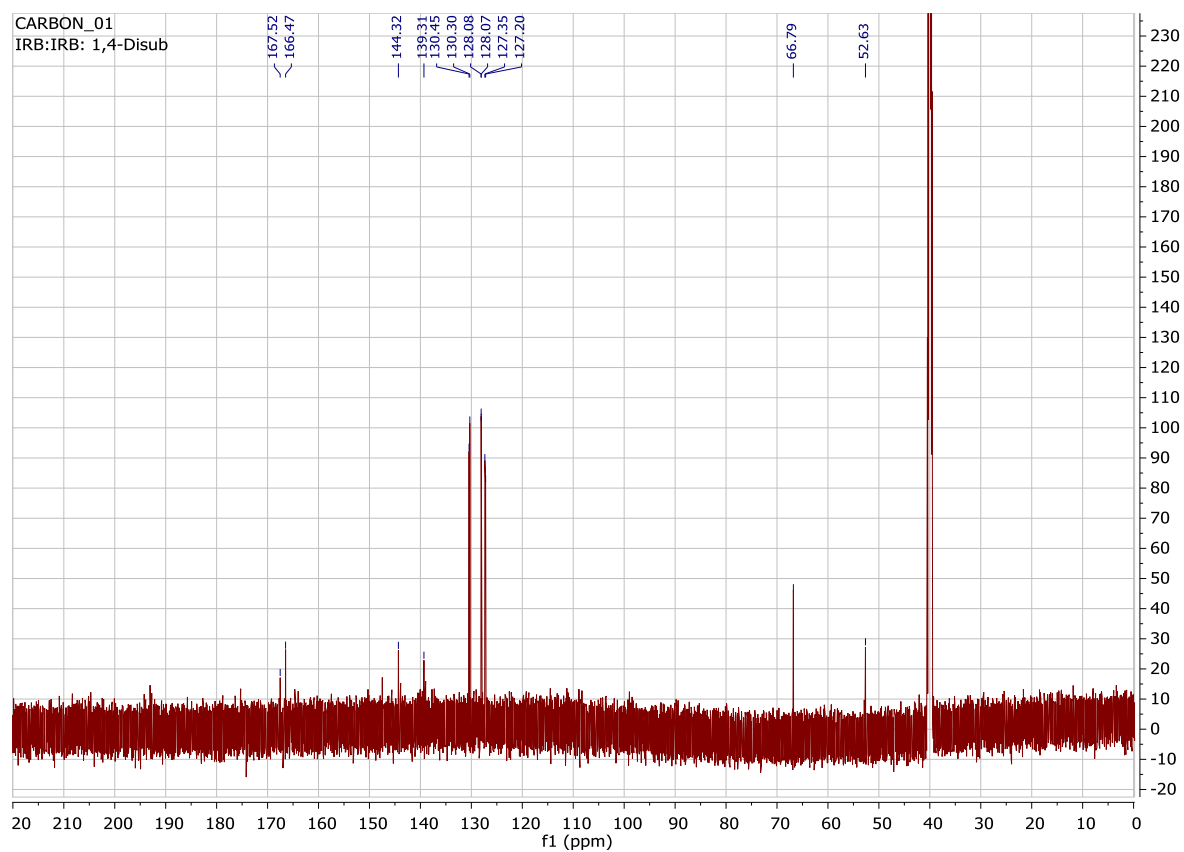
Very insoluble compound 700 MHz NMR with extended scan range for ^{13}C :



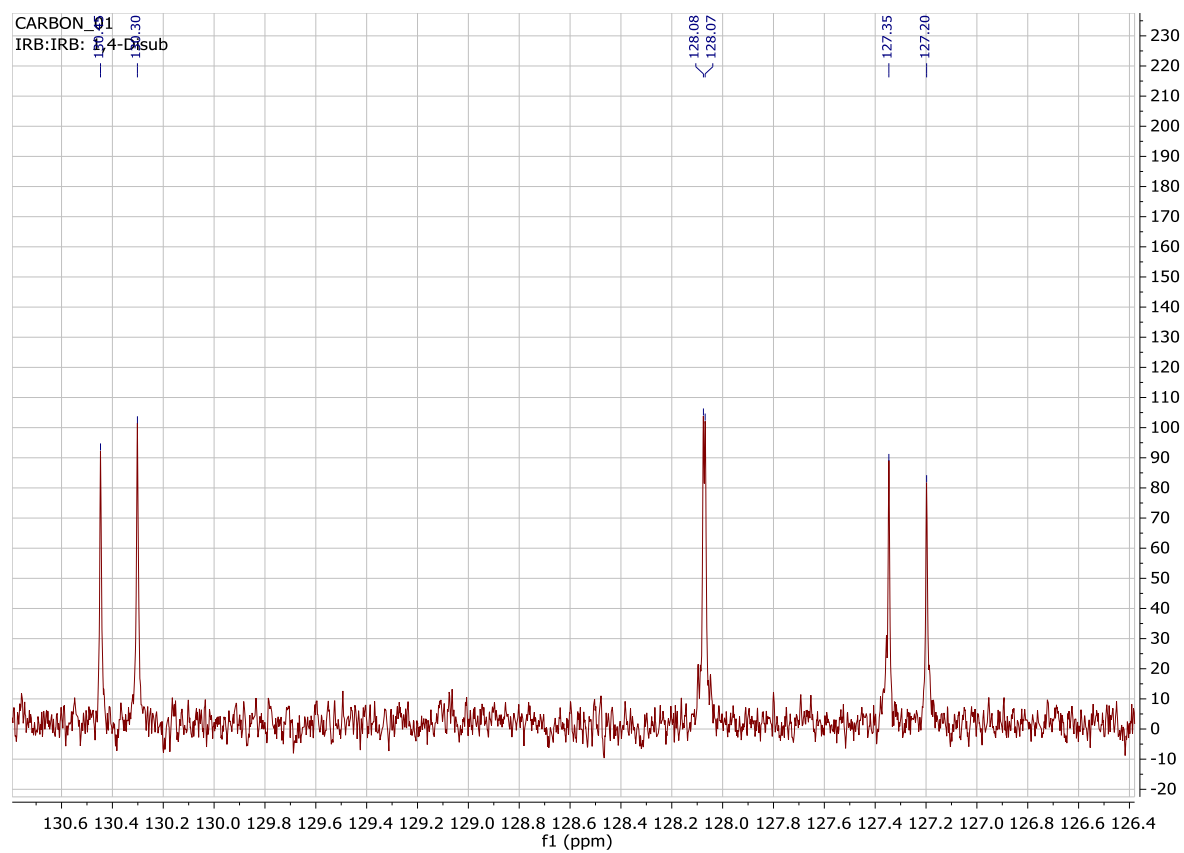
Expanded ^1H region showing the aromatic area.



RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives

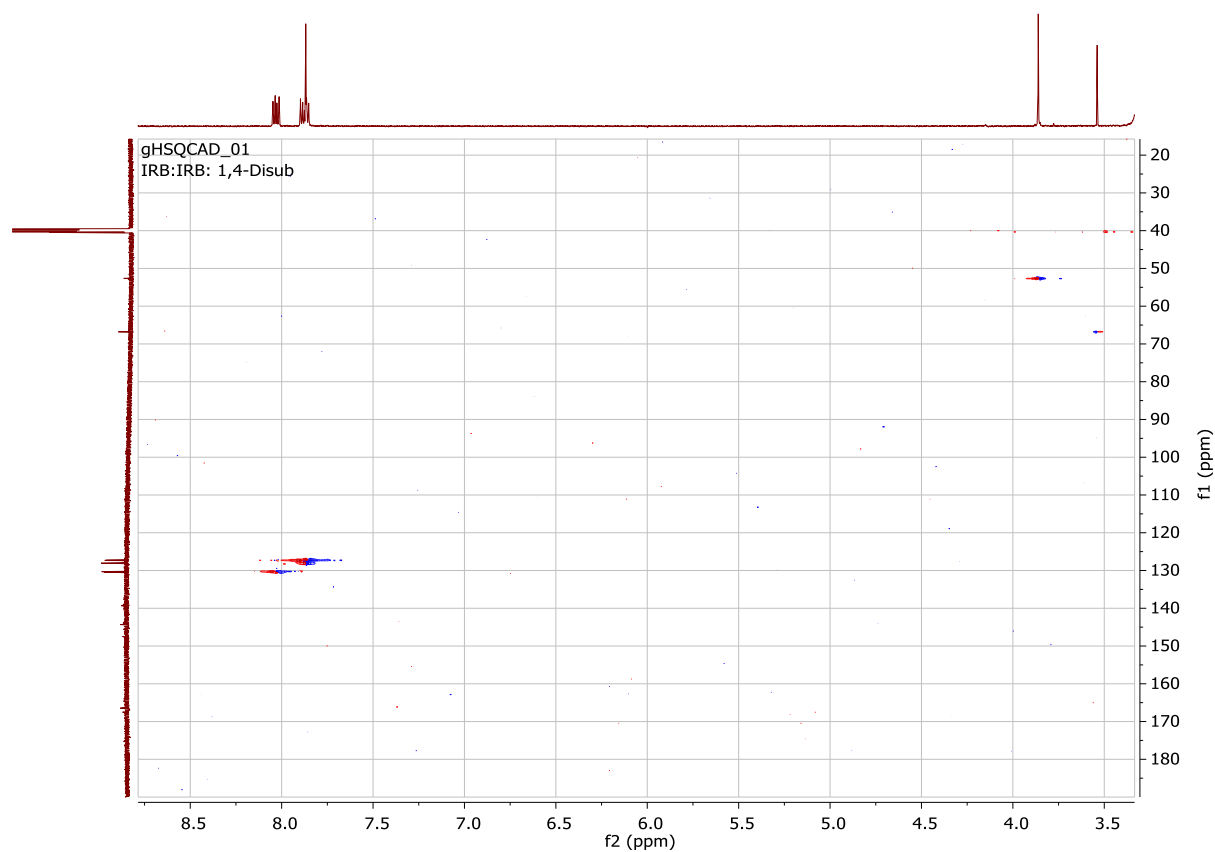


Expanded ^{13}C CH region showing splitting of signals.

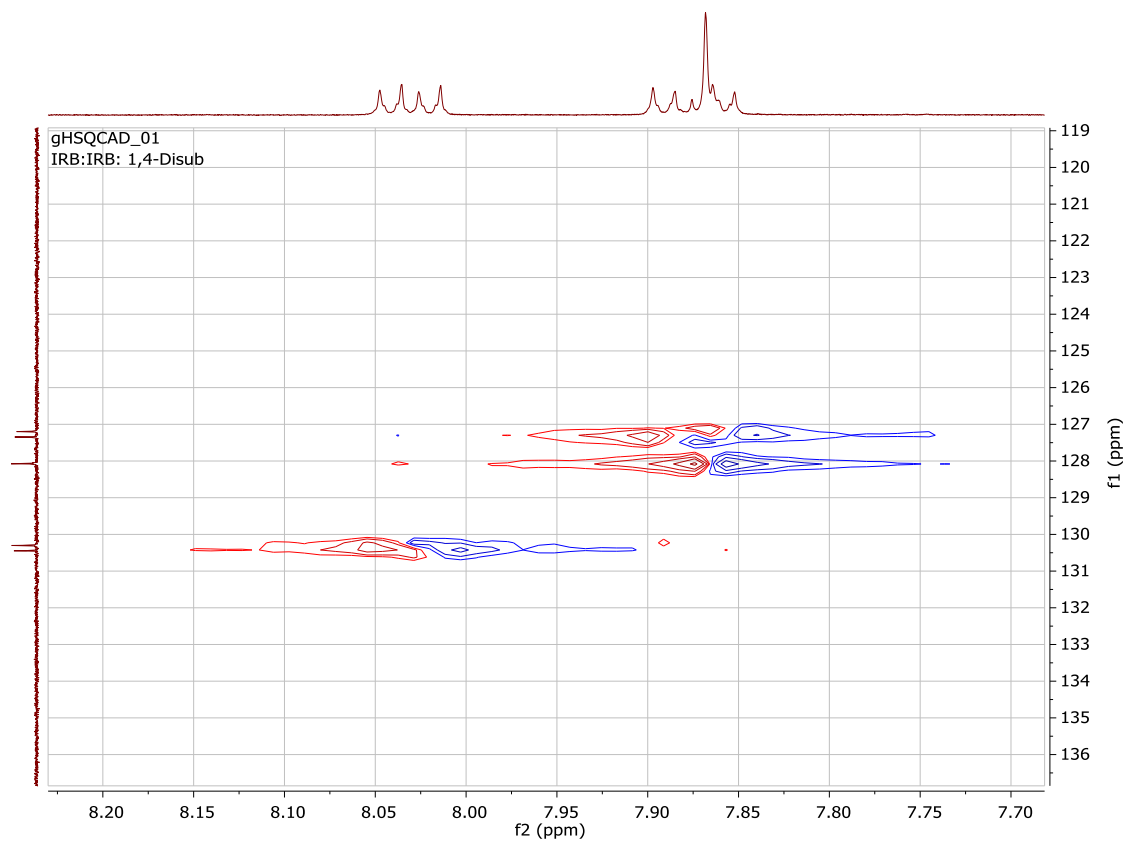


HSQC spectra

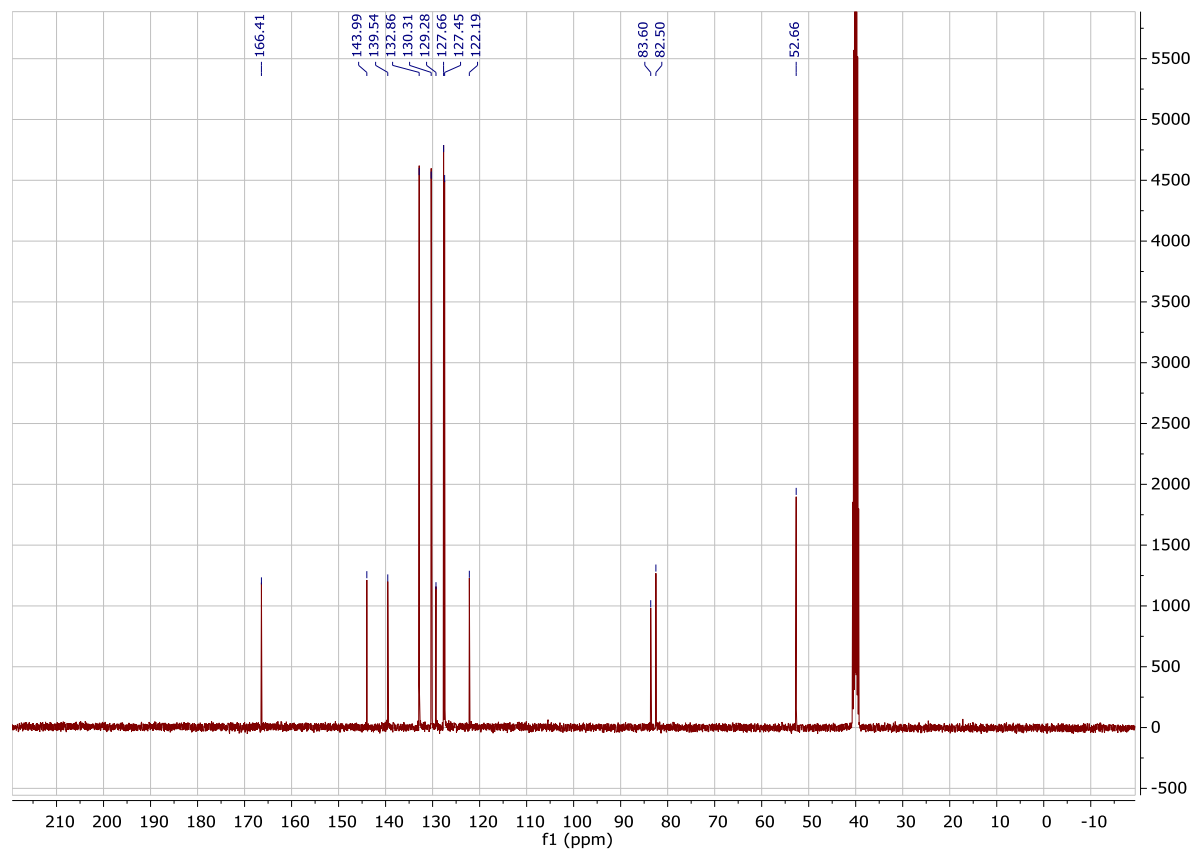
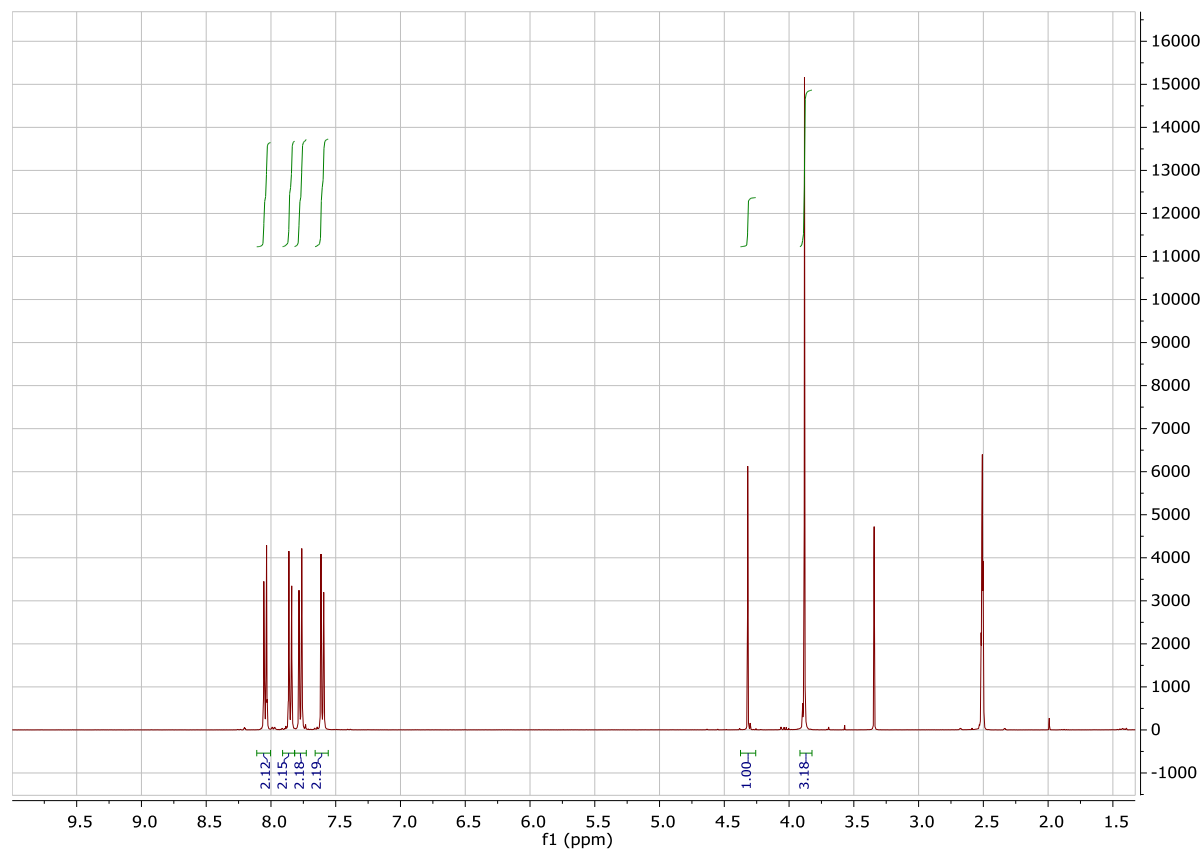
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



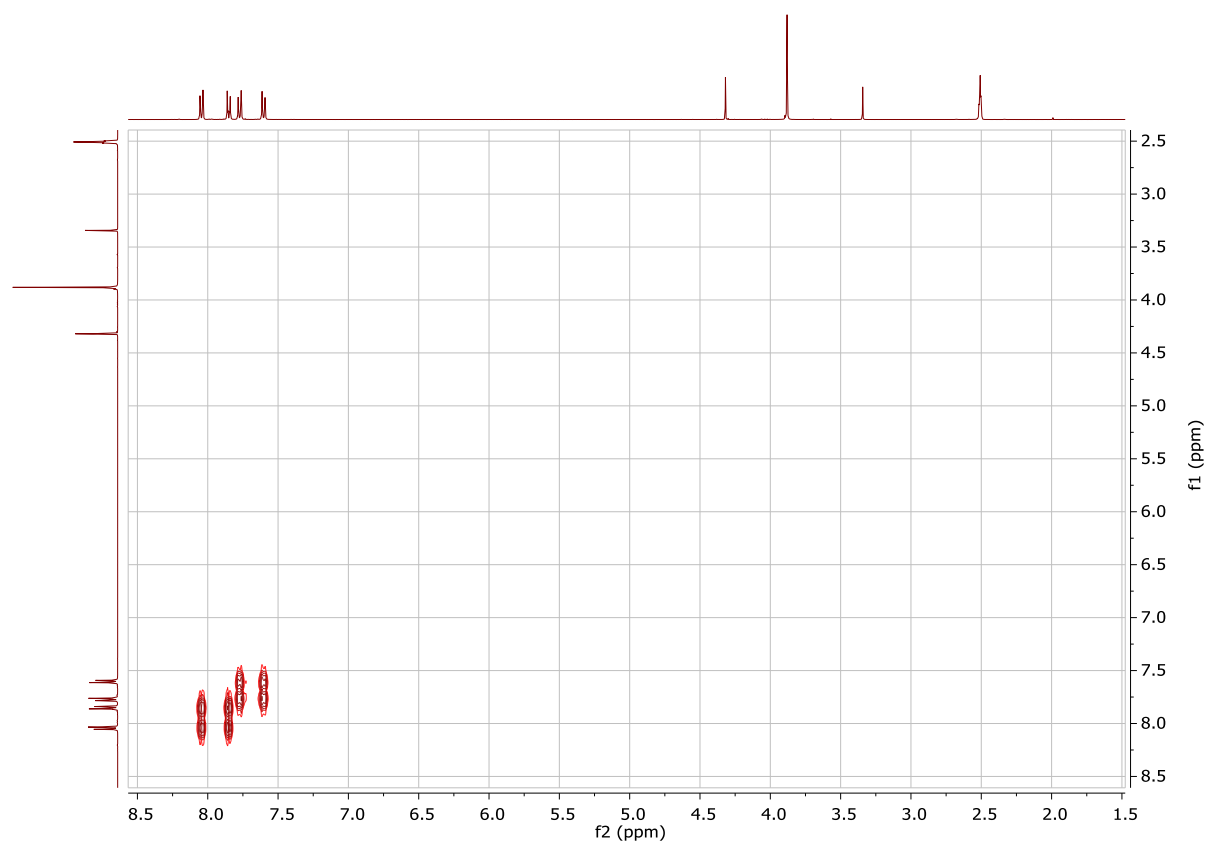
Expanded HSQC with dept colour editing



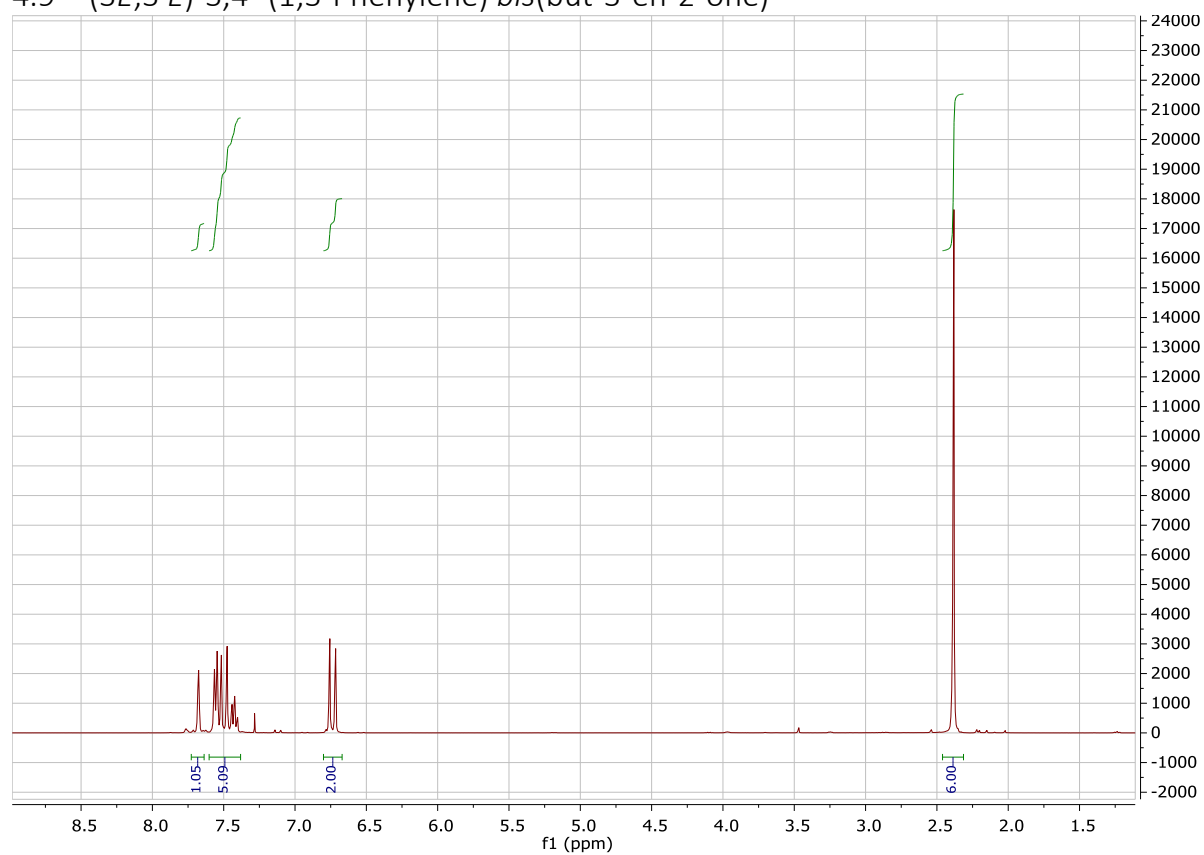
4.8 Methyl 1,1'-biphenyl-4-ethynyl-4''-carboxylate



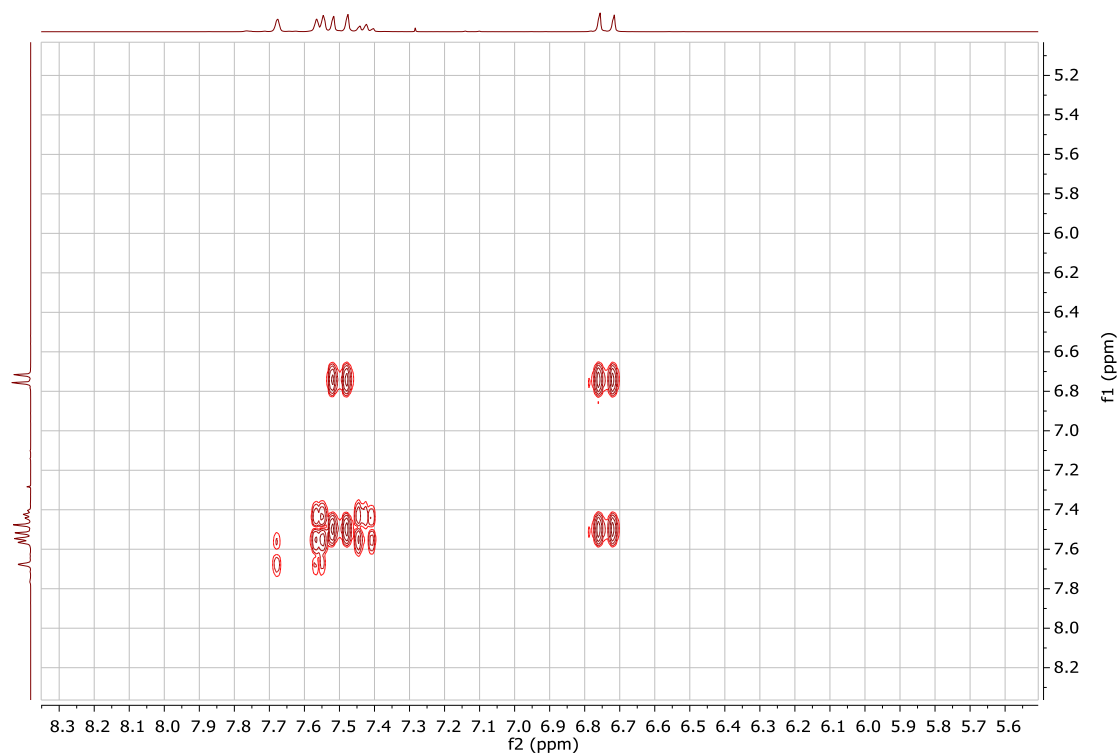
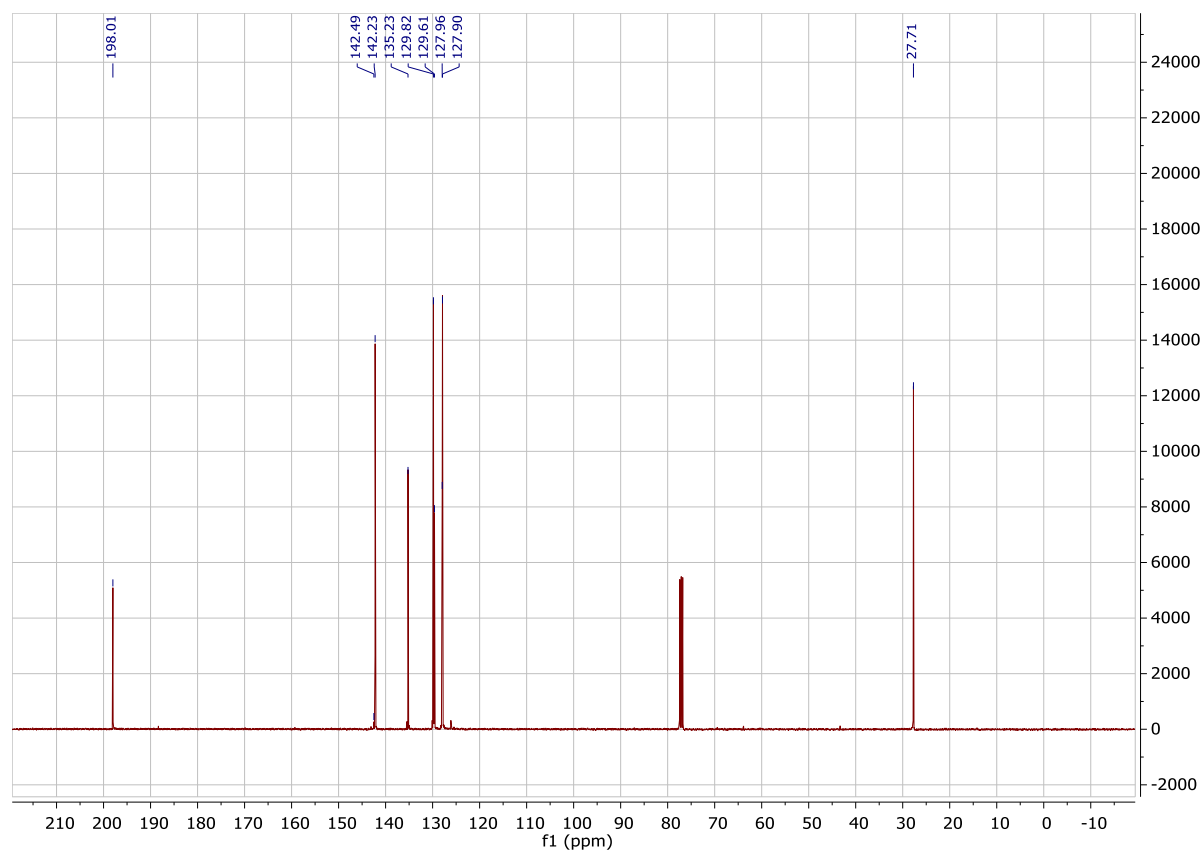
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



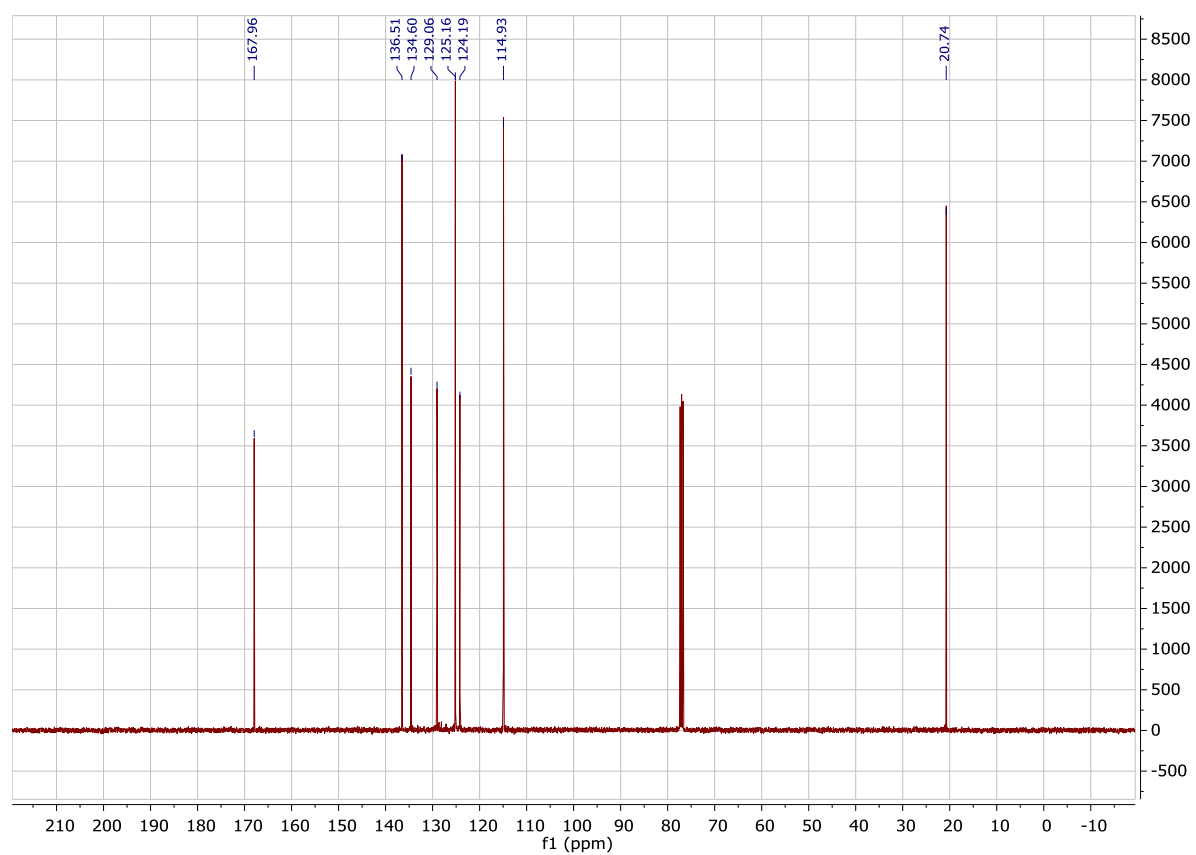
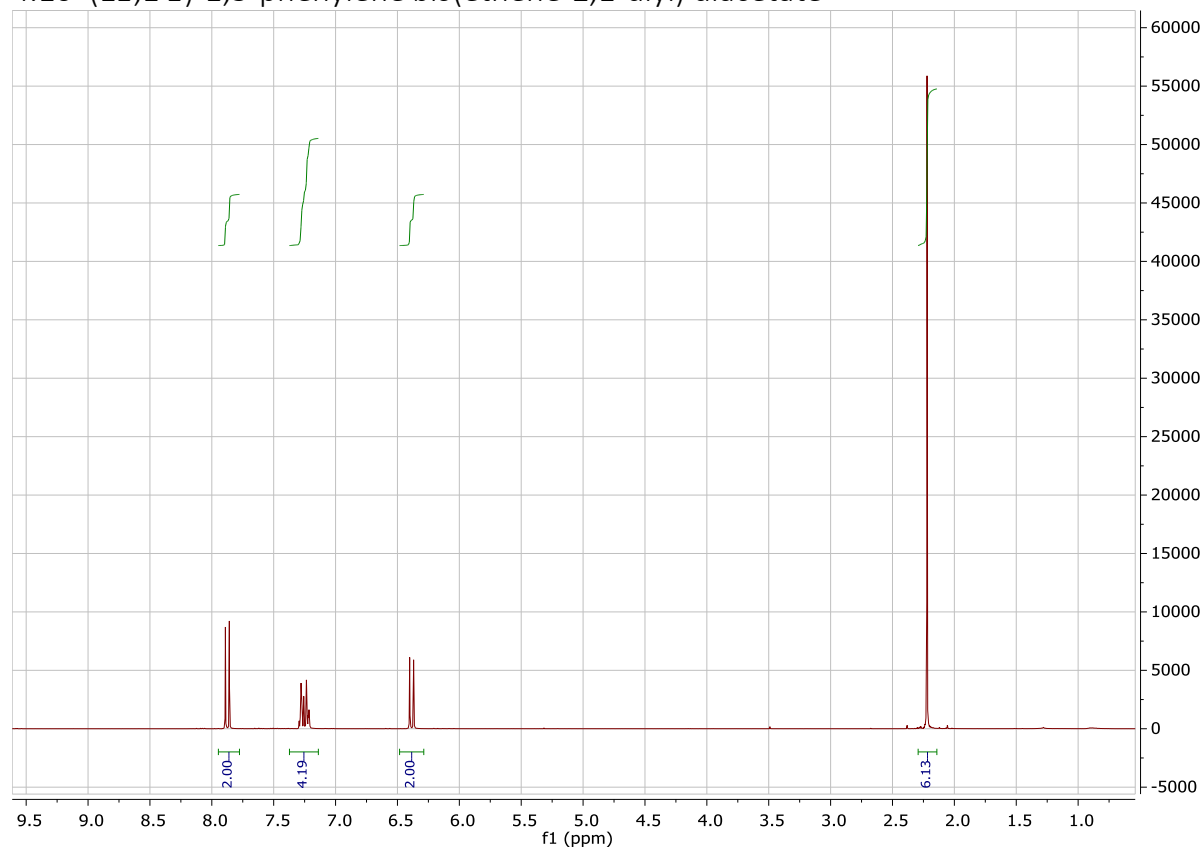
4.9 (3E,3'E)-3,4'-(1,3-Phenylene) bis(but-3-en-2-one)



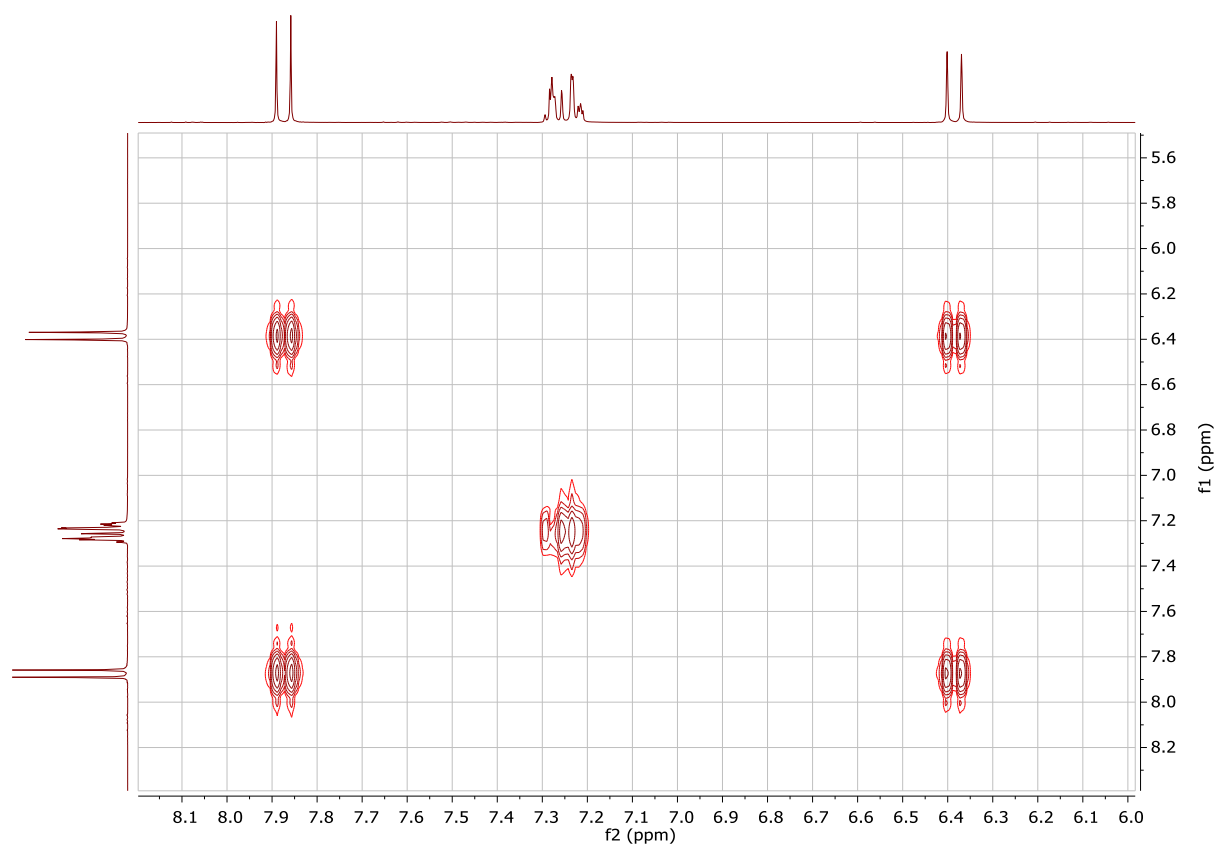
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



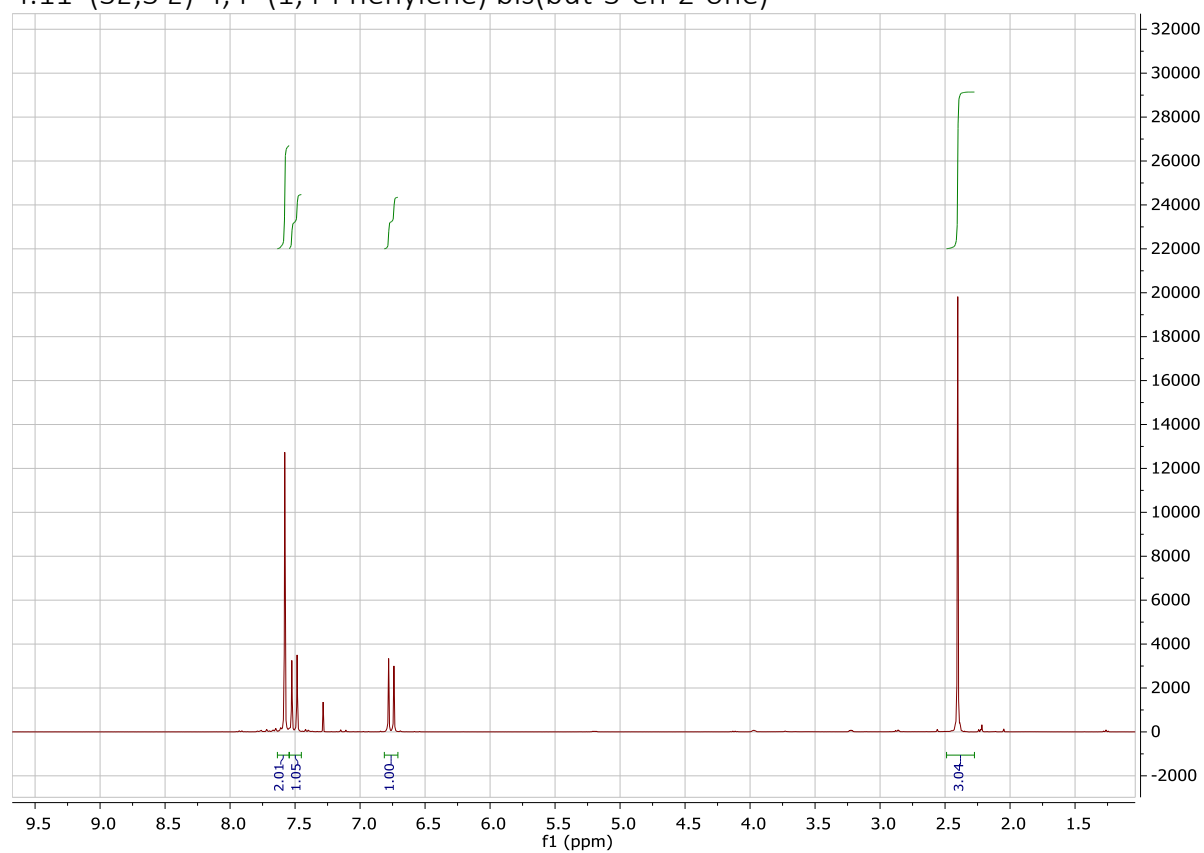
4.10 (1E,1'E)-1,3-phenylene bis(ethene-2,1-diyl) diacetate



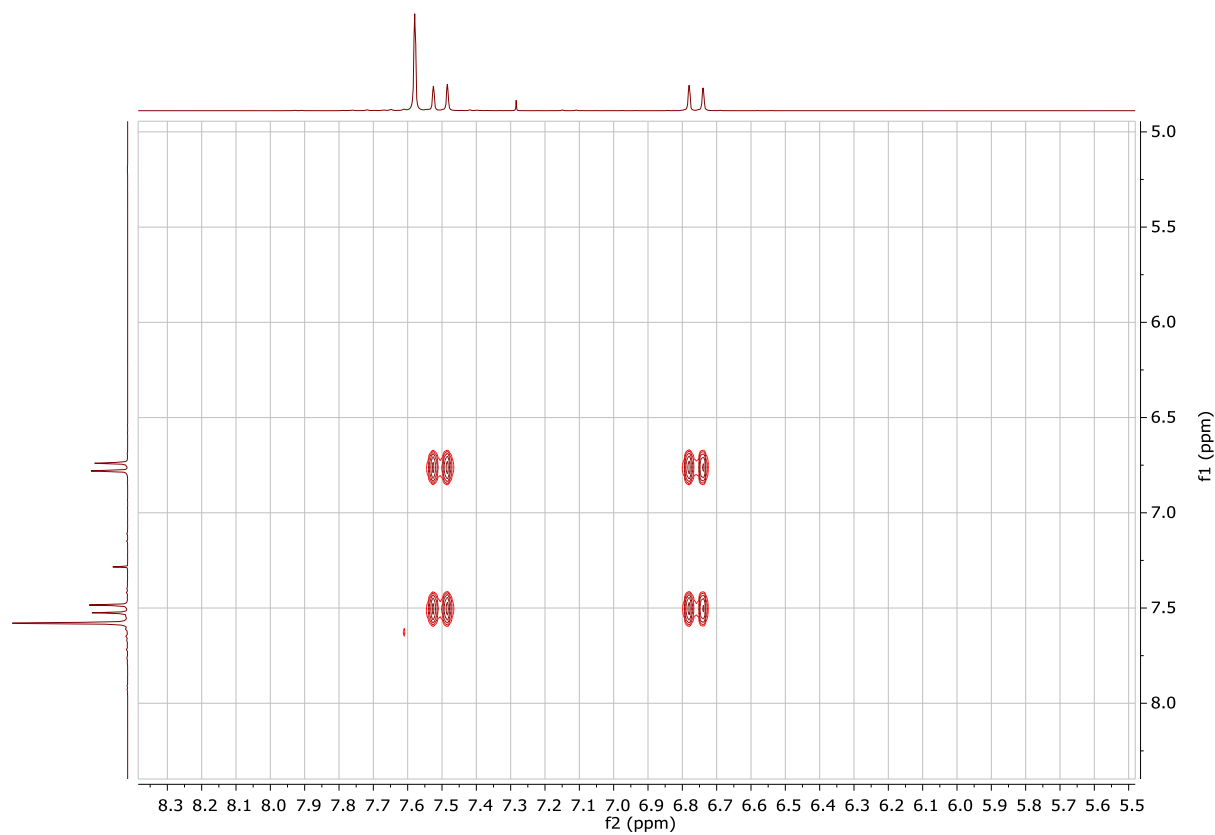
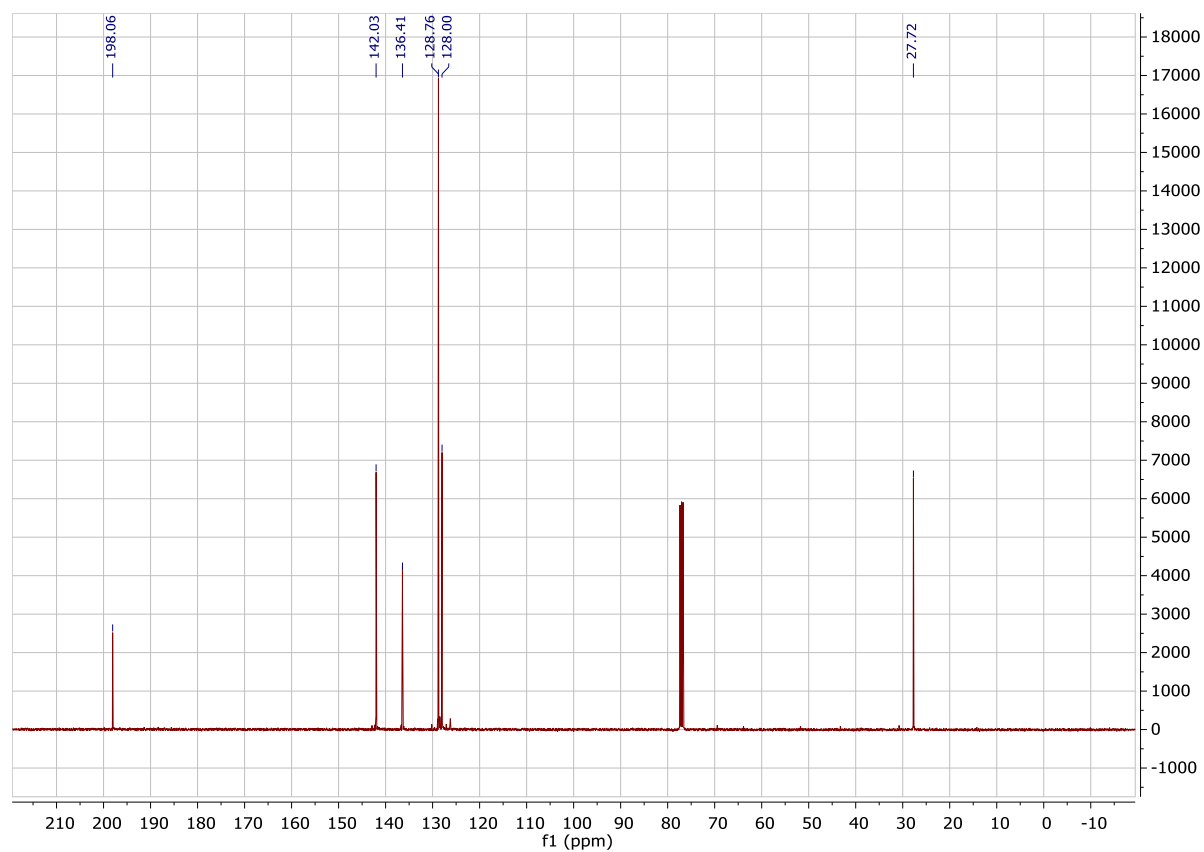
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



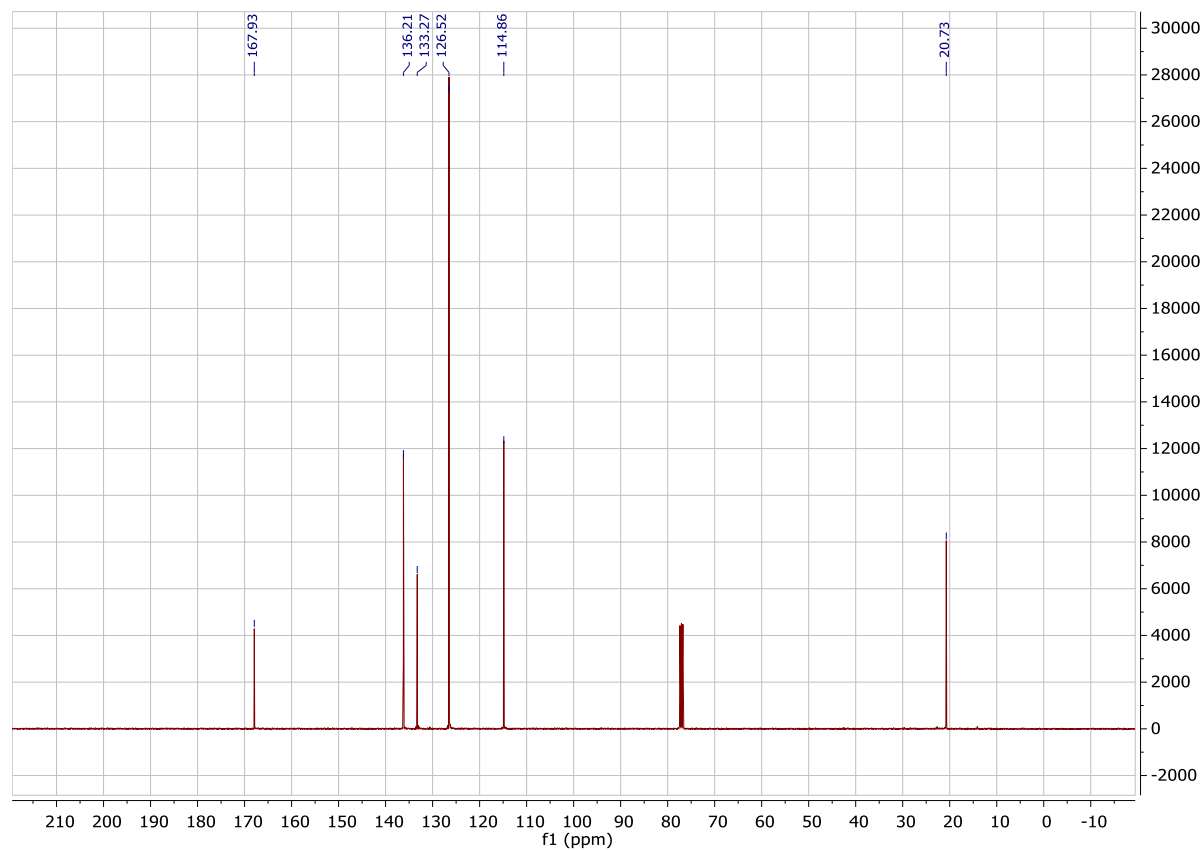
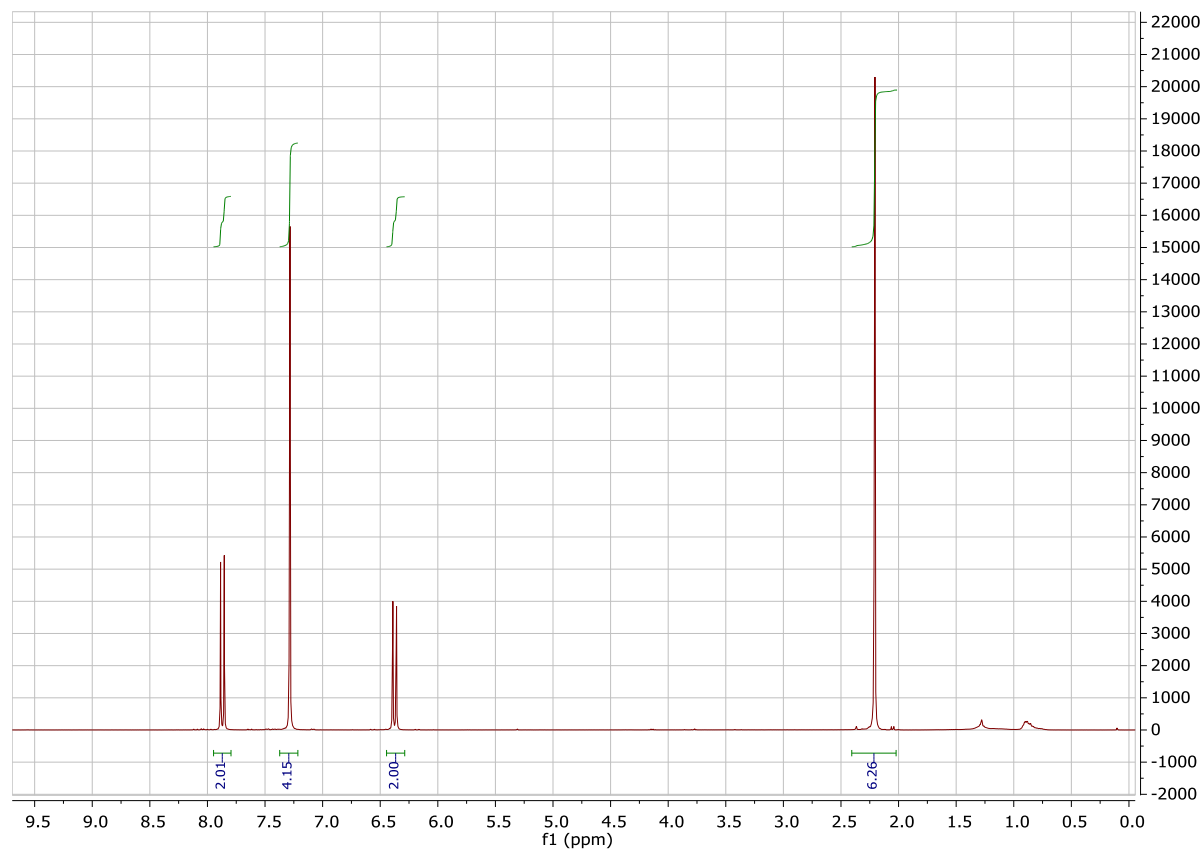
4.11 (3*E*,3'*E*)-4,4'-(1,4-Phenylene) bis(but-3-en-2-one)



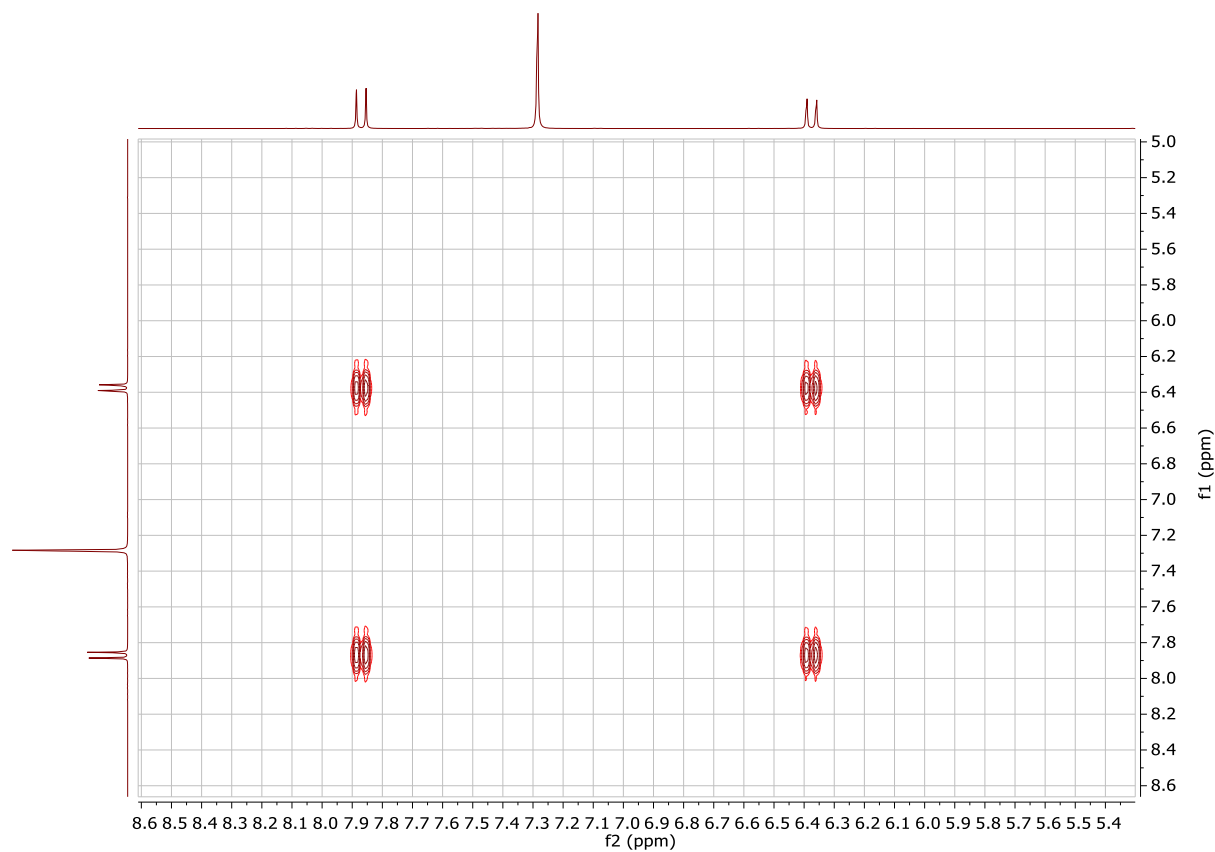
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



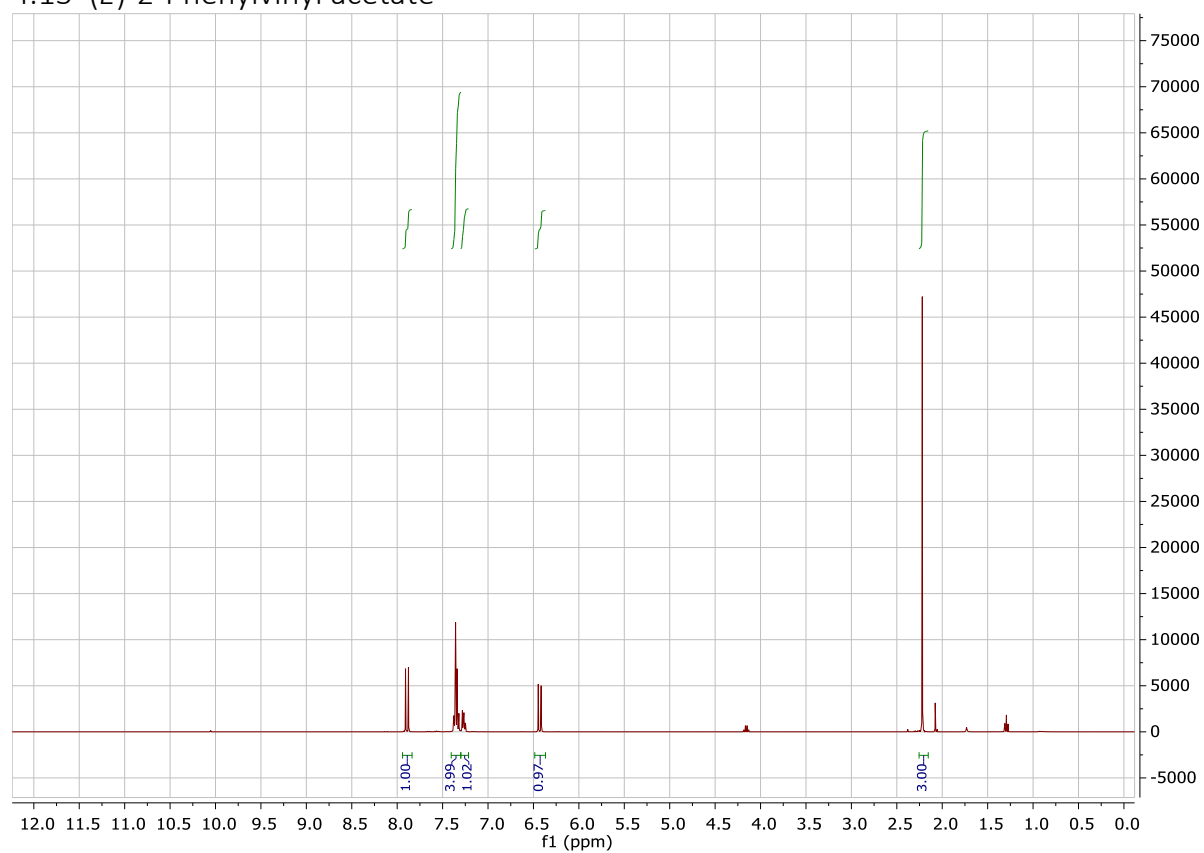
4.12 (1*E*,1'*E*)-1,4-phenylene *bis*(ethene-2,1-diyl) diacetate



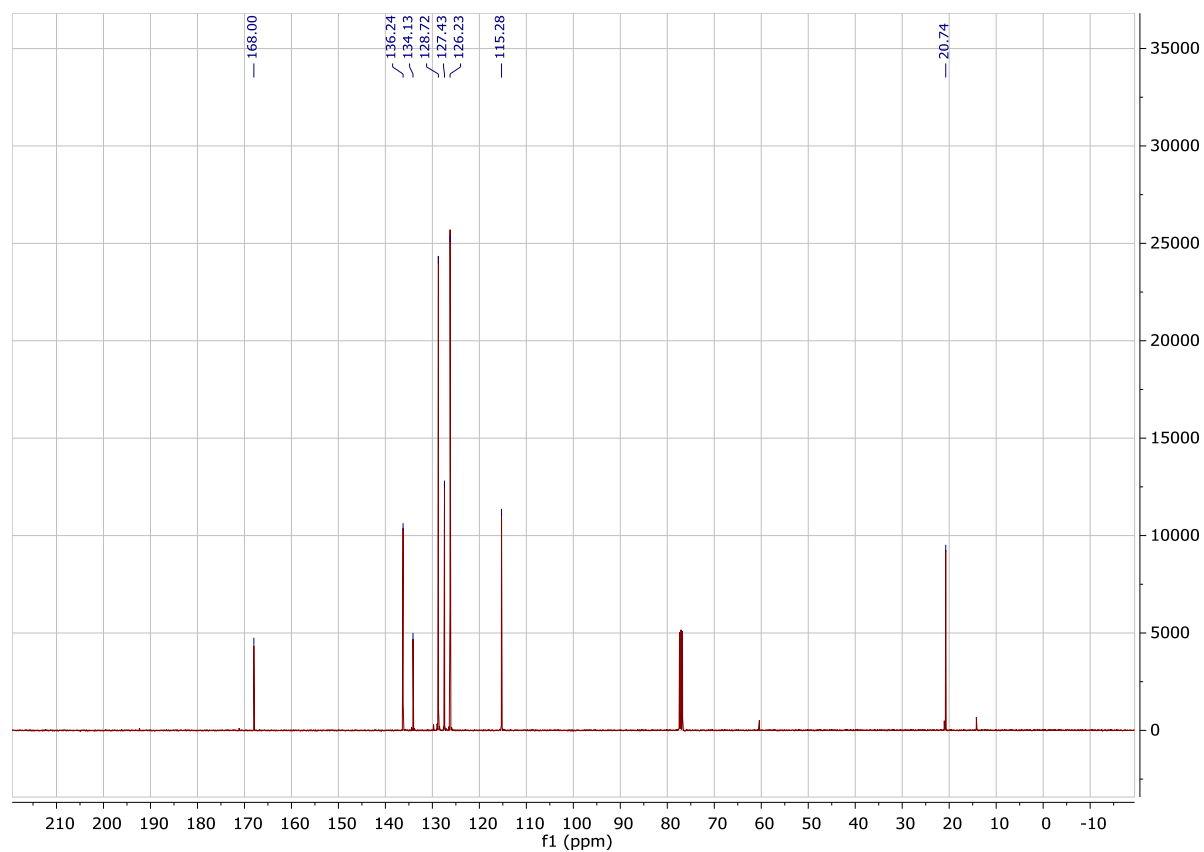
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



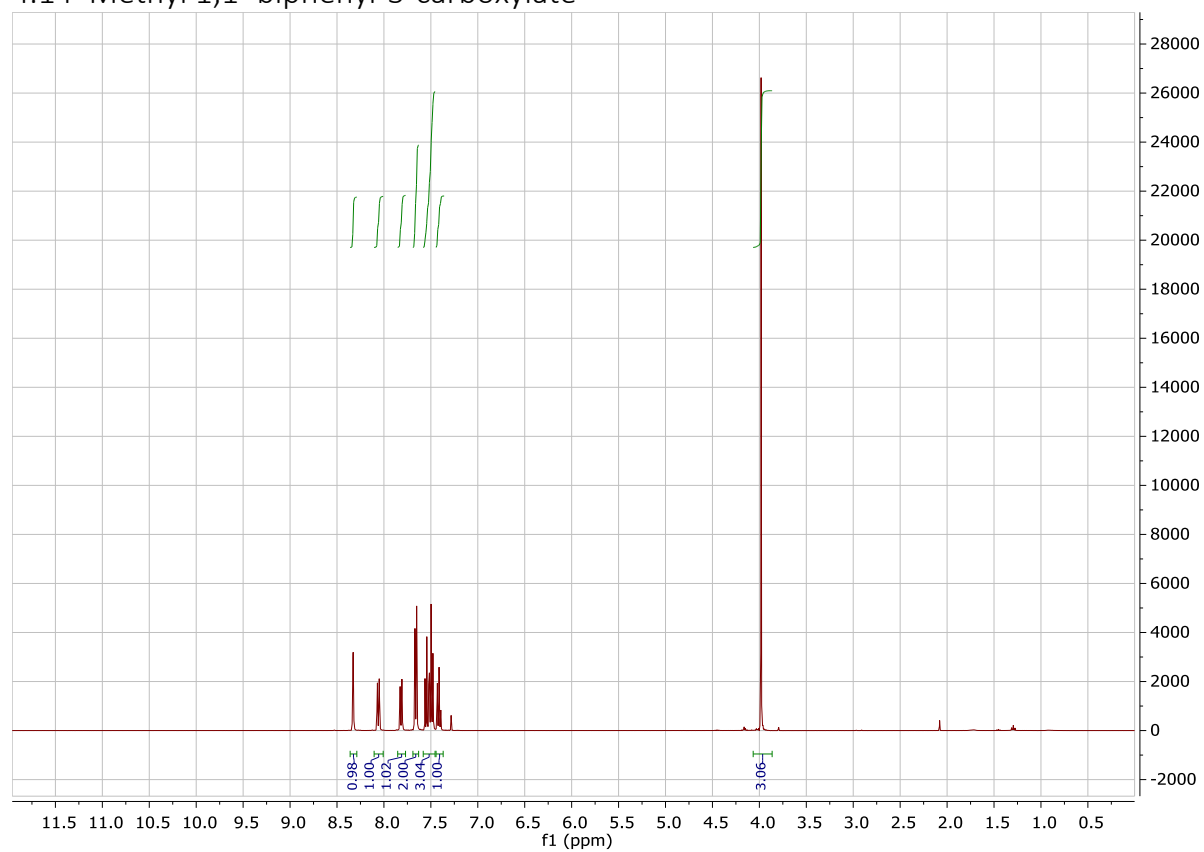
4.13 (*E*)-2-Phenylvinyl acetate



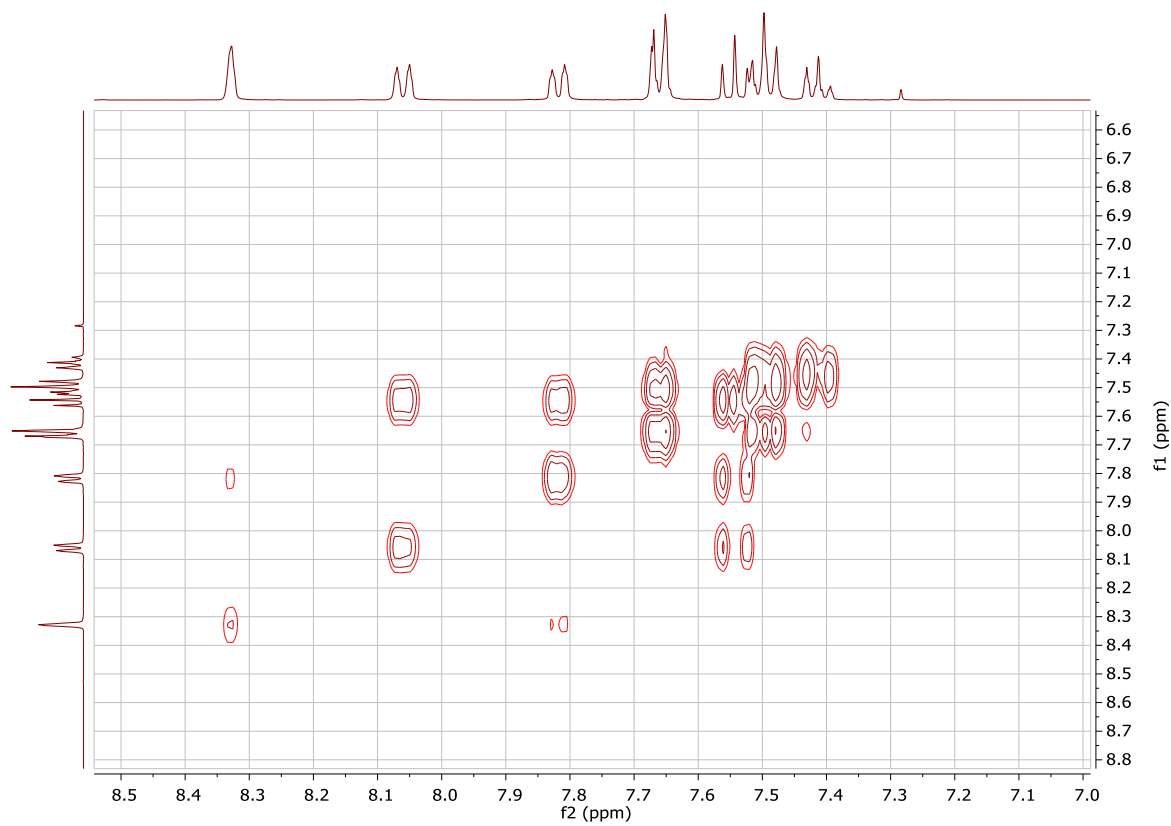
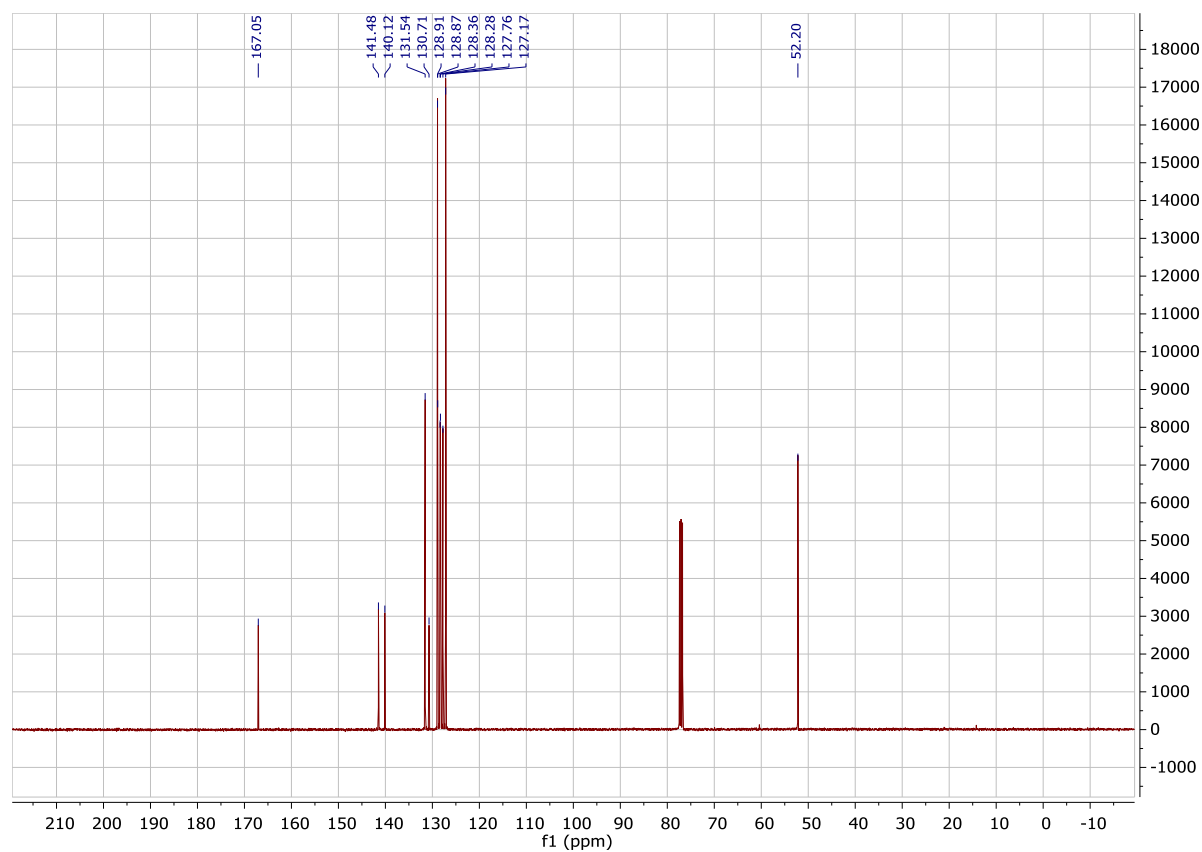
RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



4.14 Methyl 1,1'-biphenyl-3-carboxylate



RCE: Continuous Flow Synthesis of Coumalic Acid and its Derivatives



5 References

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